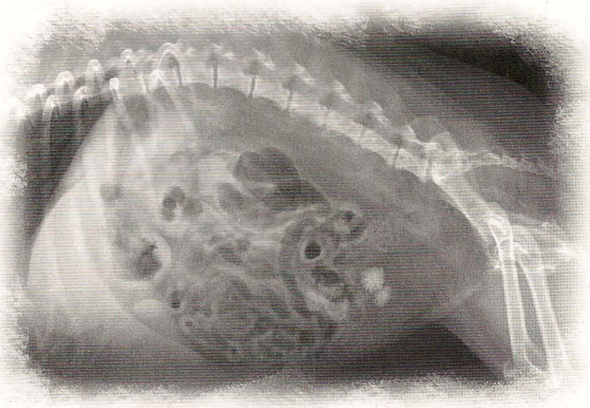
A Colour Handbook of

URINARY STONES IN SMALL ANIMAL MEDICINE

Albrecht Hesse
Reto Neiger



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A Colour Handbook of

Urinary Stones in Small Animal Medicine

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PREFACE

For a long time urolithiasis in animals was regarded as a rare condition which was of no consequence after the removal of the stones. It was only when the condition became more frequent and the urinary stones were analysed routinely with, for example, infrared spectrometry in the 1980s that veterinary medicine realized the great variety of urinary stones.

In dogs and cats in particular we find all the varieties of urinary stones that occur in humans. The logical next step was to examine the lessons from human medicine and search whether there are similar processes in pathogenesis, therapy, and prophylaxis of recurrence in small animal urolithiasis.

It soon became obvious that there are many similarities between urolithiasis in humans and animals, but there are also marked differences. Pathogenesis of urinary stones varies between species and breeds, their genetics, metabolism and nutrition. Research in the last 25 years recognized numerous causes for lithogenesis and developed therapy concepts accordingly. But during this time the composition of stones changed too, particularly in dogs and cats. Where struvite had been the dominant component it is now calcium oxalate. This change represents new challenges for science and for pet food manufacturers. We now have specific foods and drugs to prevent recurrence of urinary stones which should be supplied immediately after removal and analysis of the stones.

This book has been written based on the analyses of animal urinary stones undertaken at the Department for Experimental Urology, Clinic for Urology, University of Bonn, since 1978. We also incorporated several scientific publications about urolithiasis in animals with wide references to current international publications.

Therefore we would like to thank in particular the PhD students and colleagues who contributed to this veterinary research from 1978–2003:

Wilhelm Hicking, Georg Sanders, Mathias Brühl, Jenni Hoffmann, Michaela Nährig, Claudia Graf, Marion Wolters, Marina Frenk, Hans-Jürgen Steffes, Anke Schneider, Brigitte Baer, Ekkehard Krajewski, Helmut Orzekowsky.

Cooperation between the Clinic for Urology, University of Bonn, and the Small Animal Clinic, University of Giessen, made it possible to achieve a format for this book which makes the scientific data accessible and suitable for use in a veterinary practice.

Royal Canin, represented by J. Lindenberg and Dr. F. Conrad, supported us generously and made wide distribution of this book possible.

We hope that this book will provide useful advice on the therapy of urinary stones to the veterinary surgeon as well as the pet owner.

Albrecht Hesse and Reto Neiger

ABBREVIATIONS

ACTH	adrenocorticotrophic hormone
AGT	alanine glyoxylate aminotranferase
AP	activity product
APRT	adenine phosphoribosyltransferase
BRI	BONN risk index
CNS	central nervous system
FeLV	feline leukaemia virus
FIP	feline infectious peritonitis
FIV	feline immunodeficiency virus
FLUTD	feline lower urinary tract disease
FUS	feline urological syndrome
GR	glyoxylate reductase
IVU	intravenous urography
NSAID	nonsteroidal anti-inflammatory drug
PCR	polymerase chain reaction
PH	primary hyperoxaluria
PTH	parathyroid hormone
PTH-rP	parathyroid hormone-like protein
RSS	relative supersaturation

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CHAPTER 1

Overview of urinary stones

Epidemiology

Formation of urinary stones in various breeds of dog and cat in Europe and America

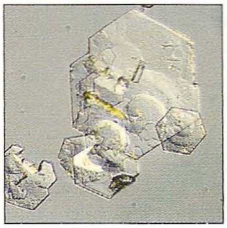
Shape, colour, and composition of urinary stones in small animals

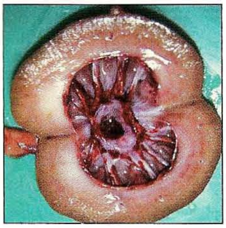
Causes of urinary stone formation

Theories on the crystallization of urinary components

Urinary stone analysis

General clinical diagnosis and treatment of urinary stones





Epidemiology

HISTORY

The earliest urinary stone ever found in a human was a bladder stone discovered in the skeleton of a young man in a grave near El Amrah in Egypt (4800 BC). Urinary stones have also been found in ancient Indian graves (3000 BC). Urolithiasis was probably the cause of the clinical signs of such historical figures as Heinrich II, Holy Roman Emperor, who had a bladder stone surgically removed in 1000 AD, Erasmus von Rotterdam (1466–1536), Michelangelo (1475–1564), Martin Luther (1483–1564), Pope Innocent XI (1611–1689), Napoleon III (1808–1873), and Johann Wolfgang von Goethe (1749–1832).

Animals have been suffering from urinary stones long before the arrival of humans. The oldest stone ever discovered was found in a marine reptile that lived in the Mesozoic Era (approximately 80 million years ago). Calcium carbonate (calcite) urinary stones, which are typical of herbivores, have been positively identified in the skeleton of an Ice Age bear (Pleistocene epoch) found in the Erpfinger Cave, southern Germany. Herodotus (484–420 BC) and Aristotle (348–322 BC) were the first to describe the occurrence of kidney and bladder stones in sacrificial animals.

Evidence has since been found of stones in the urinary systems of virtually all animal species. Urolithiasis can be a significant welfare and economic problem, particularly when they occur in food-producing animals, those raised for competitive purposes (sheep, goats, cows, and horses), and in pets (dogs, cats, rabbits, and guinea pigs).

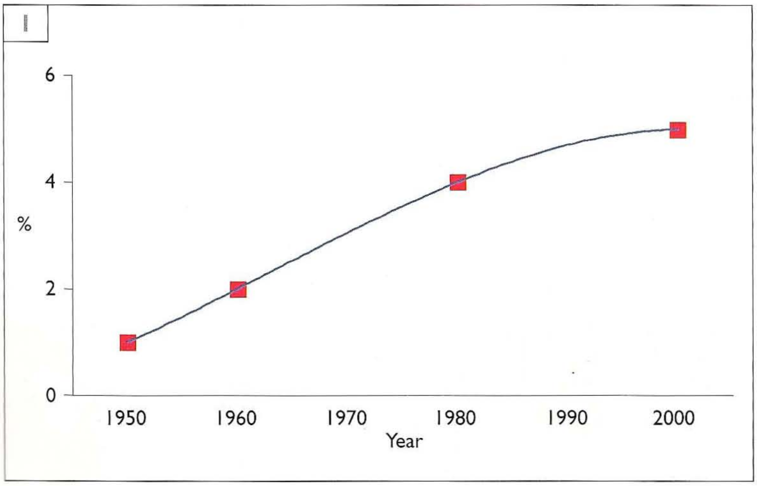
HUMANS

Urolithiasis became pandemic in the twentieth century, particularly in industrialized countries. In 2000, the prevalence rate in Germany was 5% (**1**), and 10% of all men aged over 50 had had one or more urinary stones. In both sexes, the disease primarily occurs between the ages of 30 and 50 years (**2**).

In the USA, over a 20-year period, the prevalence of urolithiasis increased from 3.8 to 5.2%.[2] Reliable data from Italy and Japan indicate an increase in the frequency of urinary stones in the population. The majority of the various forms of urinary stone that occur in humans (*Table 1*) can also be found in animals.

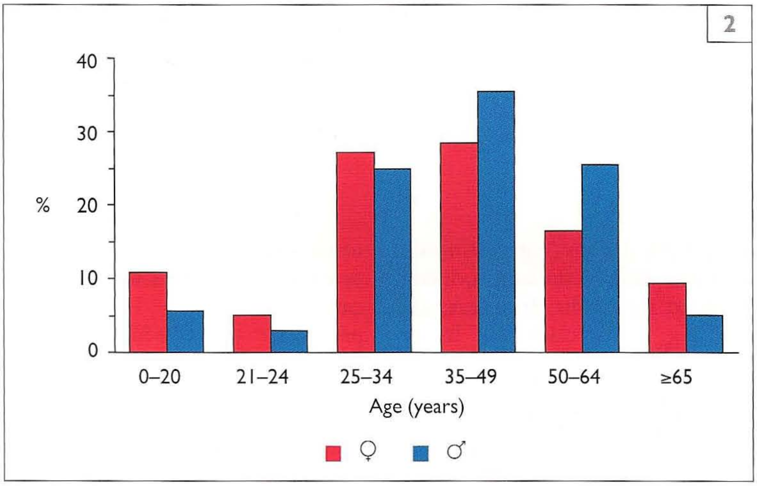
Mineralogical names are frequently used in urinary stone analyses, as these substances also occur in the mineral kingdom and analogous analytical procedures are followed. The minerals were often named after those who discovered them,[4] e.g. whewellite from William

1



1 Increase in the prevalence of urolithiasis among humans in the second half of the twentieth century.[1]

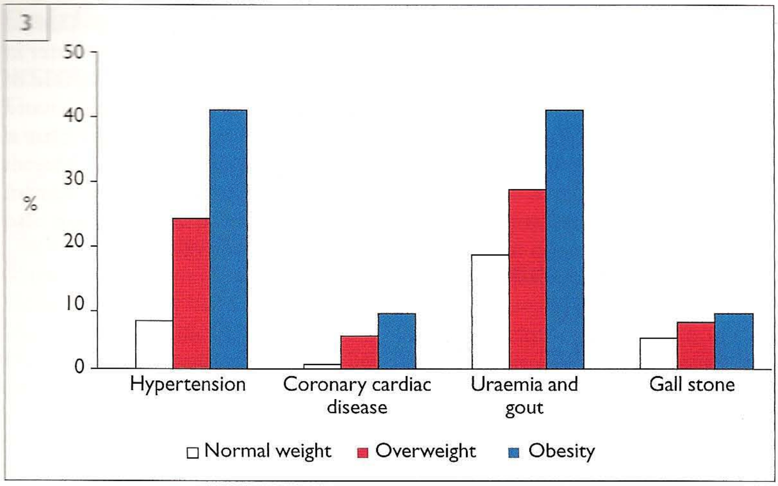
Whewell (1794–1866), weddellite from James Weddell (1787–1834), struvite from Count Heinrich von Struve (1772–1851), and brushite from George J. Brush (1831–1912). Other urinary stones were named after the place of their discovery or appearance, such as uric acid, which was first found by Scheele in 1776 in urine and in urinary stones, and cystine, which was discovered by Wollaston in 1810 in a human bladder stone and was described as 'cystic oxide'. Lassaigne confirmed the existence of this substance 13 years later in the bladder stone of a dog. The description of xanthine can be traced back to the Greek word xanthos (yellow), as the saltpetre acid that it contains gives it a yellow colour. Marcet discovered the first xanthine stone in a human. It was not until 1968 that xanthine was also found in the urinary stone of a dog.[5]



2 Epidemiological study[1] demonstrating the age dependency for the onset of disease connected to urinary stones (%) in humans.

Table 1 The most frequent types of urinary stones in humans and their percentage distribution.[3]

	Chemical name	**Mineral name**	**Frequency (%)**
Oxalate	Calcium oxalate monohydrate	Whewellite	50–60
	Calcium oxalate dihydrate	Weddellite	15–20
Phosphate	Carbonate apatite	Dahllite	5–6
	Calcium hydrogen phosphate dihydrate	Brushite	1–2
	β-tricalcium phosphate		<1
	Hydroxyl apatite	Whitlockite	<1
	Magnesium ammonium phosphate hexahydrate	Struvite	6–8
Uric acid, urate	Uric acid	Uricite	10–12
	Uric acid dihydrate	-	2–3
	Monoammonium urate	-	<0.5
	Monosodium urate monohydrate	-	Rare
Stones associated with congenital metabolic disorders	L-cystine	-	<1
	Xanthine	-	Rare
	2.8-dihydroxy adenine	-	Rare



3 Concomitant diseases in humans with calcium oxalate stones.[6]

Hereditary genetic defects (e.g. cystinuria), urinary tract infections (e.g. urease-producing bacteria), acquired metabolic disorders, and malnutrition (e.g. hypercalciuria, hyperoxaluria, and hyperuricosuria) have been shown to cause urinary stone formation in humans. Urinary obstruction resulting from anatomical anomalies can be a significant factor in urinary stone formation. A wide variety of causes is responsible for the formation of the most common types of stone, the calcium oxalates (whewellite and weddellite), which are therefore classified as multifactorial events. Insufficient urinary volume, high intake of animal protein, a diet high in milk or milk products, obesity, stress, reduced physical activity, and high alcohol consumption with systemic acidosis can all play a major role. In human medicine, urolithiasis is typically a disease of affluence, with a positive correlation to the metabolic syndrome (diabetes mellitus type II, gout, high blood pressure, hyperlipaemia, and so on) (**3**).

DOGS

There is no reliable data about the prevalence of urolithiasis in the dog. However, according to the literature, the incidence rate was around 3–5% between 1980 and 2000. Of all the dogs seen in consultation at a small animal clinic in North America between 1980 and 1993, 0.53% had urolithiasis.[7] According to a survey of 133 German veterinary practices, the frequency of urinary stones among dogs treated over a 1-year period was 0.5–1.0%.[8] A German survey of canine diseases in 1999–2001 revealed a prevalence of 0.15% (87 cases of urolithiasis out of 58,025 diagnoses). Struvite stones were found in 2.6% of dogs in a closed colony of pure-bred Beagles (55 out of 2,125) over a 17-year period.[9] A breed-related predisposition for urinary stone formation among dogs in Germany can be derived from a comparison of the 12 breeds most commonly affected by urinary stones and the statistics for puppies of those breeds between 1994 and 2004 (*Table 2*).

There has been an increase in the incidence of urinary stones in recent years, with a higher prevalence in certain breeds.

Yorkshire Terriers, Poodles, Dalmatians, Cocker Spaniels, Shih Tzus, and Pekingeses have a positive predisposition to urolithiasis, whereas German Shepherd Dogs have a negative predisposition to urinary stones.

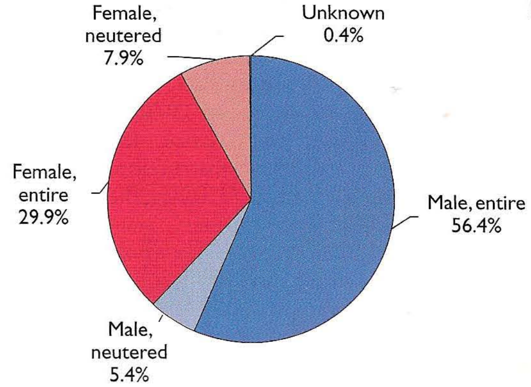
In a partially published study, the prevalence of urinary stones was found to be higher in male animals (male:female= 1.8:1).[8] However, this can differ considerably with the breed of dog and type of stone (see Chapter 2). Interestingly, urinary stones were seen less frequently in neutered dogs (**4**).

The average age of dogs with urinary stones was 7 years (range: <1–18 years), 72% of the dogs afflicted were 4–10 years old (**5**).

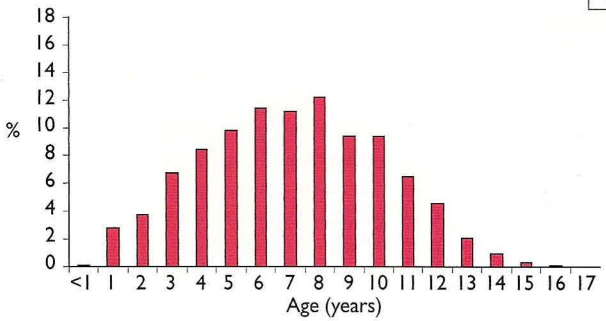
Table 2 Breed disposition of urolithiasis in dogs in Germany, comparison with puppy statistics from the German Canine Breeding Association.[8]

Dog breeds with urinary stones 1984–2001		**Puppy statistics 1994**	**Puppy statistics 2004**	
	%	%	%	
Dachshund	22.4	14.3	17.2	(+)
Yorkshire Terrier	12.7	1.2	1.8	+
Poodle	6.4	2.3	2.7	+
Dalmatian	6.2	1	1.1	+
Cocker Spaniel	6	2	2.1	+
Shih Tzu	3.1	0.34	0.52	+
Pekingese	2.9	0.09	0.18	+
West Highland White Terrier	2.7	1.5	2.4	
Miniature Schnauzer	2.2	1.2	1.1	
Sheepdog	1.8	21.4	25.5	–
Standard and Giant Schnauzer	1.9	1.4	1.7	
Bernese Mountain Dog	1.4	1.5	1.3	
(130 breeds, 6,312 dogs with urinary stones)		(190 breeds, 114,690 puppies)	(224 breeds, 92,601 puppies)	

+ Statistically predisposed to stone development
– Stone development statistically unlikely



4 Male/female distribution of dogs with urinary stones, 1984–2001 (n = 7,658).[8]



5 Age distribution of dogs with urinary stones, 1984–2001 (n = 7,563).[10]

Almost all stones are found in the lower urinary tract (bladder 60%, urethra 16%, bladder/urethra 23%).[8] Among male dogs, 43% of all urinary stones occurred only in the bladder, in 32% of cases both the bladder and urethra were affected, and in 25% the stones were found only in the urethra. Among female dogs, as expected, only a small number of urinary stones were found in the urethra (10%). Irrespective of gender, only about 1% of all stones occurred in the upper urinary tract (*Table 3*). Some reports, however, indicate that stones, especially calcium oxalate, are more common than originally thought in the kidney and in the ureter.[8] Modern imaging techniques play a major role in refining the diagnoses.

CATS

In studies at the Pathology Institute of the Veterinary Medical Faculty of Dresden in 1862–1897, urolithiasis occurred in 0.22% of cats.[11] A German study into feline disorders in 1999–2001 confirmed a prevalence of 0.27% (107 cases of urolithiasis in 39,760 diagnoses). The obstruction of the urethra with a crystalline, pasty material is a common clinical finding in later reports. The term FUS (feline urological syndrome) was coined in 1970 by Osbaldiston and Tausig to describe the syndrome with dysuria, urethral obstruction, stone formation, and haematuria.[12] Today, the term FLUTD (feline lower urinary tract disease) is preferred, which covers the whole clinical picture, including urinary stones. However, a distinction should always be made between urethral plugs and crystalline stones.

Specific, epidemiological data for urolithiasis in cats are not yet available. According to studies in the USA and UK, the incidence of FLUTD is 0.85–1.5%.[13,14] Today, it is estimated that 8–10% of cats will suffer from FLUTD on one or more occasion(s) in 10 years.[15] It is consequently assumed that FLUTD can occur in all breeds of cat.

In one study of 143 cats with haematuria and dysuria (FLUTD), both urinary stones and urethral plugs, frequently with mineralized inclusions, were found in 22% of cases.[14] The inclusions were predominantly struvite (76%).

Twenty-one different breeds were included in a study of 1,797 urinary stones from cats (1981–2000).[8] According to the population distribution, 62.3% of those stones came from European Shorthairs and 25% were from Persians, reflecting a probable specific breed disposition.

Urinary stones are more common in neutered cats than in intact cats, which is not the case in dogs. Male cats are overrepresented (**6**). There is no clear gender predisposition among intact animals.

In a European study, the average age of afflicted cats was 6.6 years (range: <1–18 years).[16] Fifty-six percent of the patients were 1–6 years old (**7**). In the American literature, this age group represents 80% of affected subjects.[17]

Nearly all stones were located in the lower urinary tract: bladder 70%, urethra 11%, bladder/urethra 15%. Renal or ureteral stones are rare, accounting for just 1% of cases. Fifty-seven percent of the stones in neutered tomcats were found in the bladder, 19% in the urethra, and 23% in the bladder and urethra. In female cats, stones were predominantly found in the bladder (>91% of cases) (*Table 4*).

In the American literature, there is mounting evidence that stones, particularly calcium oxalate stones, are also diagnosed in the kidney and can become lodged while passing through the ureters.[18]

RABBITS/GUINEA PIGS

Reports of urinary stones in rabbits and guinea pigs are usually only found in the literature as specific case studies or studies with small numbers of animals.[19-21] The loving care these animals are given by their owners and their increasingly longer life spans, amongst other things, means that urinary stones are being diagnosed more frequently.

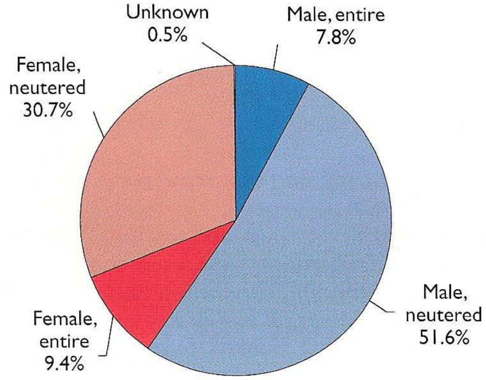
In a study of 35 rabbits with urinary stones, the average age was 3.7 years (range: 1–8 years). The gender ratio among these animals was male:female = 1.2:1; over 90% of the stones were located in the lower urinary tract.[8]

In a study of guinea pigs with urinary stones (n = 20), the average age was 4.6 years (range: 2–8 years).[22] The stones mainly occurred in female animals (female:male = 3:1). The anatomy of the urethral orifice in females results in a higher incidence of stones in the urethra, whereas bladder stones were exclusively diagnosed in male animals.

Table 3 Location of urinary stones (%) in dogs in Germany as a function of gender (1984–2001).[8]

	Bladder	Urethra	Bladder/urethra	Kidney	Ureter
Female (n = 2,247)	88.3	1.5	8.9	1.1	0.2
Neutered female (n = 600)	86.5	1.8	10.8	0.7	0.3
Male (n = 4,263)	43.1	24.8	31.3	0.4	0.4
Neutered male (n = 415)	41.9	24.6	32.8	0.5	0.2
Unknown (n = 10)	0.8	0	0	0	0
Total (n = 7,535)	60.0	16.0	23.1	0.6	0.3

6 Gender distribution of cats with urinary stones, 1984–2001 (n = 1,423).[16]



7 Age distribution of cats with urinary stones in 1984–2001 (n = 1,393).[16]

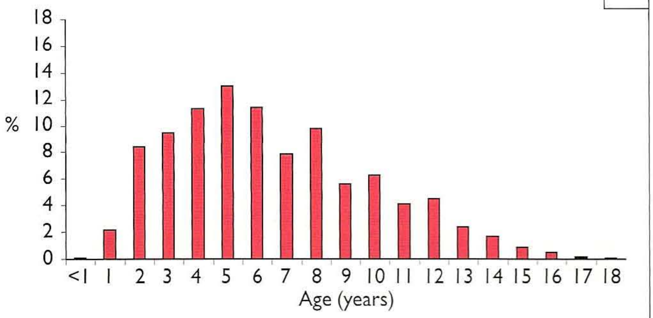


Table 4 Location of urinary stones (%) in cats in Germany as a function of gender.[8]

	Bladder	Urethra	Bladder/urethra	Kidney/ureter
Female (n = 208)	91.3	2.4	4.8	1.4
Neutered female (n = 572)	91.3	1.6	6.6	0.5
Male (n = 115)	50.4	15.7	29.6	4.3
Neutered male (n = 832)	57.1	19.2	23.0	0.7
Unknown (n = 37)	70.3	16.2	10.8	2.7
Total (n = 1,764)	72.1	11.2	15.7	1.0

Formation of urinary stones in various breeds of dog and cat in Europe and America

DOGS

Urinary stones from 4,082 dogs from 27 European countries were analysed between 1999 and 2001, and the history of the animals recorded.[8] Urinary stones were thus examined from a total of 152 breeds. *Table 5* is a comparison of the 32 commonest breeds from the nine countries where occurrence was highest. The table shows that the frequency of stones varies as a function of the breed distribution in the various countries.

Urinary stones are seen most commonly in Yorkshire Terriers, Dachshunds, and Dalmatians in Germany. In the international statistics, Dachshunds have a lower share only in Switzerland, the Netherlands, and the UK. No stones from Dalmatians were seen in Finland or the Netherlands. The Bichon Frisé is presumably very widespread in Norway and Finland; this breed has a marked tendency towards urinary stone formation. Maltese Terriers with urinary stones came exclusively from Belgium and the Netherlands. In this study, no stones were seen in Golden Retrievers, Dobermanns, Fox Terriers, Spitz, or Standard and Giant Schnauzers from any of the countries in the table.

A study in the Czech Republic examined 1,366 urinary stones from 68 breeds of dog.[23] The majority of the urinary stones came from crossbreeds (13.3%), Dachshunds (10.5%), Dalmatians (8.1%), Miniature Schnauzers (5.5%), Cocker Spaniels (5.4%), and Poodles (5.3%).

In a US study of 156 breeds of dog with urinary stones,[7] uroliths were most common in crossbreeds (20–25%), followed by Miniature Schnauzers (15–25%), Cocker Spaniels (5–10%), Yorkshire Terriers (5–8%), Bichon Frisés (5–7%), Shih Tzus (5%), and Lhasa Apsos (5%).

A Canadian study examined 16,647 urinary stones from dogs over a 5-year period.[24] The five commonest breeds in this study were the Miniature Schnauzer (14.3%), Shih Tzu (13.2%), Bichon Frisé (11.8%), Lhasa Apso (6.2%), Dalmatian (3.4%), and Yorkshire Terrier (3.1%).

A study in the Benelux states (Belgium, the Netherlands, and Luxemburg) looked at 2,900 uroliths and their distribution among 91 dog breeds. Most stones were found in Yorkshire Terriers (8.5%), Bichon Frisés (8.3%), Schnauzers (2.6%), Shih Tzus (1.8%), Dalmatians (1.8%), and Poodles (1.6%).[24a]

The most commonly affected breeds in a study of 299 calculi in Portugal were Poodles (11%), Cocker Spaniels ((9.7%), Dalmatians (8.7%), and Yorkshire Terriers (7.7%).[24b]

A paper in Mexico on 200 calculi found that mixed breed dogs were affected most (24%), followed by Schnauzers (24%), Poodles (11%), Dalmatians (4%), German Shepherd Dogs (4%), and Cocker Spaniels (4%). Similar distribution of 143 calculi was observed in Brazil: 62% mixed breed, 18% Poodles, 11.5% Schnauzers, and 10% Cocker Spaniels.

CATS

A 20-year European study examined 1,797 urinary stones from cats from 16 countries. Besides Germany (53%), the highest numbers of stones were received from the Netherlands (7.8%), Italy (2.9%), Switzerland (2.7%), Finland (1.8%), Austria (1.7%), and France (1.5%).[8]

The commonest breeds with urinary stones were the European Shorthair (62.3%) and the Persian (25%), followed by Chartreux (1.5%), Siamese (1.4%), British Shorthair (1.2%), Maine Coon (1.0%), and the Norwegian Forest Cat (1.0%).

A US study of 17,218 urinary stones from cats (1981–1997) from more than 30 breeds[25] was characterized by an overrepresentation of Himalayans (10.0%), Persians (9.6%), and Siamese (2.8%), in addition to a group of European Shorthairs and crossbreeds (74%).

A similar distribution of cat breeds with urinary stones was reported in Canada:[26] 68.4% European Shorthair, 18.9% European Longhair, 5.5% Himalayan, 5.5% Persian, and 2.4% Siamese.

A study carried out in the Benelux states reported urinary stones from 15 cat breeds (77% European Shorthair, 11 % Persian).[24a]

Table 5 Breed distribution among dogs with urinary stones (1999–2001) in nine European countries. The 32 commonest breeds from 27 countries are shown (only seven breeds from Finland, as the Australian and Norwich Terriers and the Finnish Lapphund are underrepresented in the overall statistics)

Number of stone analyses	**Total** n = 4,082	**Germany** n = 1787	**Italy** n = 429	**Finland** n = 392	**Netherlands** n = 364	**France** n = 270	**Switzerland** n = 137	**UK** n = 118	**Norway** n = 93	**Belgium** n = 91
Breeds	%	%	%	%	%	%	%	%	%	%
1 Crossbreed	16.78	18.00	28.90	5.40	11.54	6.70	19.00	11.90	5.40	5.49
2 Yorkshire Terrier	11.34	12.10	15.60	2.60	12.36	18.50	13.90	10.20		16.48
3 Dachshund	5.59	10.60			4.40		2.90	4.20		
4 Dalmatian	5.93	8.10	6.30			3.70	5.10	7.60	3.20	5.49
5 Shih Tzu	4.65	4.20	7.00		4.40	11.10		5.90	4.30	12.09
6 Poodle	3.26	2.30	1.90		4.40	9.30	3.60		3.20	6.59
7 Miniature Schnauzer	2.99	2.40		7.90	4.67		2.90		9.20	
8 Bichon Frisé	2.99			13.50		4.40		6.80	29.00	3.30
9 West Highland White Terrier	2.98	4.30			3.57		2.90	5.10	3.20	
10 Cocker Spaniel	2.01	1.80				3.30				
11 Pekingese	1.89		1.90			2.60	3.60			
12 Maltese	1.81				9.89					9.89
13 Jack Russell Terrier	1.64				4.40			6.80		
14 Golden Retriever	1.35									
15 Cairn Terrier	1.30				3.02					
16 Dobermann	1.25									
17 German Shepherd Dog	1.15		1.90						2.20	
18 Fox Terrier	1.15									
19 Lhasa Apso	1.15					4.10		4.20		
20 Rottweiler	1.13									2.20
21 Bernese Mountain Dog	1.08	1.70					3.60			
22 Standard and Giant Schnauzer	0.93									
23 Labrador Retriever	0.91							6.80		2.20
24 Papillon	0.91			3.80			4.40		3.20	
25 Pug	0.81		1.90							
26 English Bulldog	0.78									3.30
27 Spitz	0.73									
28 Cavalier King Charles Spaniel	0.73								3.20	
29 Basset Hound	0.71		1.90			2.20				
30 Welsh Corgi	0.71			6.10						
31 Pinscher	0.66		2.60							
32 Griffon	0.61			3.80						
Total proportion (%)	81.91	65.50	69.90	43.10	62.65	65.90	61.90	69.50	66.10	67.03
Breeds, total (n)	152	108	52	73	60	47	46	36	38	32

Shape, colour, and composition of urinary stones in small animals

In small animals, most stones are located in the bladder, and their shape indicates that it is also the site of their formation. Solitary stones are therefore usually rounded in shape, whilst the presence of several stones results in them being worn down. Rapid formation invariably gives rise to small crystals with smooth surfaces; well formed irregular crystals are usually associated with slow stone growth. There is currently no plausible explanation for why some cases present with multiple bladder stones whilst others have large solitary stones. Urinary stone formation may be linked to urinary obstructions. It is therefore likely that microliths that are flushed out of the kidney into the bladder remain suspended in the residual urine and continue to grow, producing stones of various sizes. Solitary stones probably originate in the bladder (**8**).

> The surface of the stone is determined by its composition and the rate of growth.

As pure chemical compounds, all urinary stone substances are basically white in colour. Certain types of urinary stones only acquire their characteristic colouring after the inclusion of urinary pigments (urochromes). It is noticeable that phosphates usually retain their basic white colouring, whereas purines (e.g. urates, xanthine) turn various shades of brownish red (**8**).

In both the dog and the cat, the composition of urinary stones is very similar to those found in humans (see *Table 1*), even 2.8-dihydroxy adenine was recently confirmed in a dog (see Chapter 2). However, the distribution of the various types of stone is very different in humans, dogs, and cats. Thus, just as there is a country-specific distribution of breeds of dog among which stones have been confirmed (*Table 5*), there is also a characteristic distribution of types of urinary stones in the various regions, as can be seen from the details of a European study in comparison with a large American study (*Table 6*).[8]

Calcium oxalate stones were more common in dogs and cats in the USA than in Europe, and in Europe, the ratio of whewellite to weddellite is the opposite of that seen in the USA. The incidence of brushite and cystine stones is also remarkably high among European animals in comparison with American animals; this is probably related to differences not only in breed distributions but also in nutritional and environmental factors. Interestingly, ammonium urate stones (15.5%) and sodium urate stones (7%) appear to be very common in some animals in Brazil (n = 45).[29]

Causes of urinary stone formation

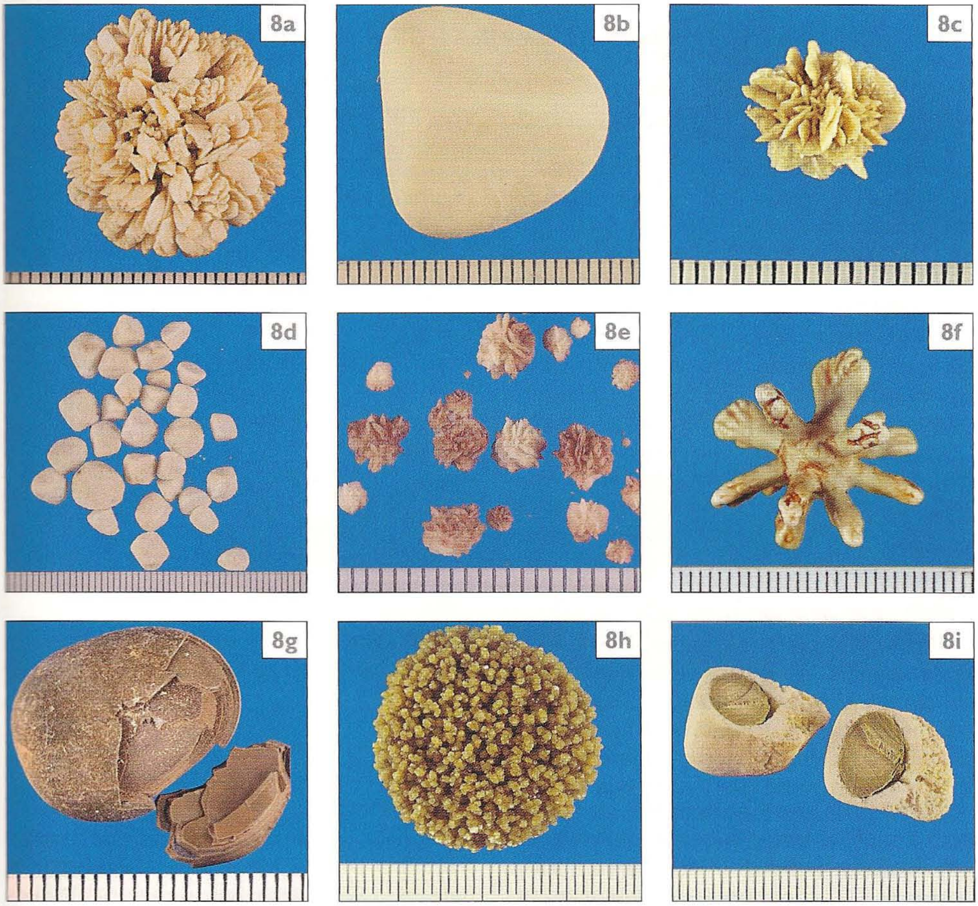
GENETIC CAUSES

There is a possible genetic predisposition for the formation of urinary stones, as there is a high tendency towards recurrence with identical results for urinary stone analysis. Some genetic causes of urolithiasis in man and animals have been established.

Cystinuria

At a frequency of 1:7,000, cystinuria is one of the most common hereditary diseases[30] in humans; it is also fairly common in dogs and has been observed in cats.[10,14,16,28,31-34] It is a recessive autosomal inherited disease, characterized in humans by the defective reabsorption of the dibasic amino acids cystine, lysine, arginine, and ornithine in the transport system in the spiral membrane of the proximal tubule. Molecular genetic studies in humans have located two types of cystinuria genes – a rBAT defect on gene SLC3A1 in chromosome 2 and an additional $b^{0,+}$AT gene on SLC7A9 in chromosome 19. The International Cystinuria Consortium has classified them as types A and B.[35]

The precise heredity of cystinuria in French and English Bulldogs also appears to be linked to the SLC3A1 and SLC7A9 genes.[36] However, other breeds with cystinuria do not appear to carry these mutations, and a different mutation is probably responsible. The mutation was long thought to be sex-linked, occurring only in male animals; however, females are also affected although to a much lesser extent. In European studies only about 2% of all cystine stones are found in female animals, which is probably a result of their anatomy. Recessive autosomal heredity has been detected in the Newfoundland[37] and is assumed to be present in other breeds.



8 Shape and colour of urinary stones. (**a**) Irregular, well formed crystals are indicative of slow-growing urinary stones (species: dog; colour: white; analysis: 100% struvite; diameter about 2 cm). (**b**) Smooth faceted surface, fine crystalline (species: dog; colour: white; analysis: 100% struvite; diameter about 2 cm). (**c**) Irregular surface, characteristic bipyramidal crystals (species: dog; colour: grey; analysis: 55% weddellite, 45% whewellite; diameter about 1 cm). (**d**) Multiple stones with smooth, faceted surfaces (species: cat; colour: white; analysis: 100% struvite; diameter 0.3–1 cm). (**e**) Multiple stones with irregular surface (species: cat; colour: grey–brown; analysis: 100% weddellite; diameter 0.1–0.8 cm). (**f**) Flail form with well formed individual crystals at the points (species: dog; colour: grey; analysis: 100% silicate; diameter 2.5 cm). (**g**) Bean-shaped, rounded, fine crystalline surface, cup-shaped structure (species: dog; colour: brownish red; analysis: 100% ammonium urate; diameter about 2 cm). (**h**) Spherical, irregular to fine crystalline surface (species: dog; colour: honey yellow; analysis: 100% cystine; diameter about 3 cm). (**i**) Smooth, fine crystalline surface, spherical core (species: dog; colour: outer layer white, core brownish red; analysis: mantle 100% struvite, core 100% xanthine; diameter about 1.5 cm).

Table 6 Comparison of the percentage distribution of types of urinary stone in the dog and the cat in Europe and the USA (1980–2000).[10,16,27,28]

Type of stone	Dog Europe (n = 7.697) %	USA (n = 77.191) %	Cat Europe (n = 1.413) %	USA (n = 9.481) %
Struvite	58.3	49.6	65.3	47.6
Calcium oxalates	15.3	31.4	24.7	39.6
- whewellite	5.9	22.9	9.3	31.4
- weddellite	9.4	8.5	15.4	8.2
Brushite	2.3	0.2	0.8	0.1
Calcium phosphate	0.4	0.6	3.2	1.0
Ammonium urate	6.7	6.8	3	6.1
Sodium and potassium urate	0.3	0.7	0.1	0.1
Uric acid	<0.1	<0.1	-	0.1
Cystine	13.4	1.0	0.6	0.3
Xanthine	0.3	0.1	0.5	0.1
Silicate	0.2	0.9	0.2	-
Rarities/Matrix	0.3	1.1	1.6	1.4
Drugs	<0.1	<0.1	-	-
Mixtures	1.3	6.6	-	3.6

The assay of amino acids in the urine differs from that of humans with cystinuria. Besides the previously mentioned dibasic amino acids, cystine, lysine, arginine, and ornithine, increased levels of citrulline, taurine, threonine, cystathionine, glutamine, and glutaminic acid have also been detected in dogs with cystinuria.[31,38] In addition, dogs with cystinuria can also have carnitinuria. As a result, there is an increased risk of carnitine deficiency in these animals.[39] Urinary stone formation is also observed with normal cystine excretion if the urine is highly concentrated.

Cystine stones have been found in the maned wolf.[40] The prevalence of cystine stones in certain breeds such as the Dachshund, Chihuahua, Mastiff, Bull Mastiff, American Staffordshire Terrier, Irish Terrier, Münsterländer, English Bulldog, and Newfoundland highlights the effects of selective breeding.

Studies into the heredity of cystinuria in cats have yet to be performed. In a study of 1,797 feline urinary stones, only 11 cystine stones (0.6%) were found, nine of them in female animals.[8]

Xanthinuria

In humans, xanthinuria is a very rare disease. Xanthine stones have been diagnosed in humans in 22 countries, thus ethnic origin does not seem to be a determinant factor. However, a higher frequency of xanthine stones has been confirmed in the southern European countries.

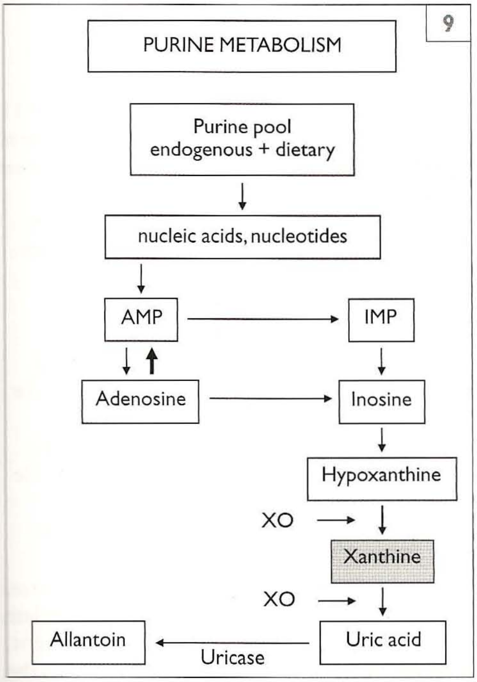
Xanthine is a product of purine metabolism, resulting from the action of the enzyme xanthine oxidase on hypoxanthine; it is then further oxidized, by xanthine oxidase, into uric acid (**9**).

Xanthine oxidase deficiency results in the increased renal excretion of hypoxanthine and xanthine. Xanthine is relatively insoluble and, at high levels in concentrated urine, it can crystallize out leading to the formation of urinary stones.

> Whereas uric acid represents the end-product in humans, in dogs and cats it is broken down further by the enzyme uricase into allantoin.

At a genetic level, three types of deficiency have been identified:[41]

- Type I: xanthine oxidase deficiency caused by a mutation in the xanthine oxidase gene on chromosome 2p22.
- Type II: xanthine oxidase deficiency and aldehydroxidase deficit.
- Type III: a mutation in the molybdenum cofactor sulphurase gene. Besides a xanthine oxidase deficiency, this results in a mild to severe neuropathy only in cases of a complete molybdenum cofactor deficiency.



9 Diagram for xanthinuria. (AMP = adenosine monophosphate; IMP = inosin monophosphate; XO = xanthine oxidase)

Types I and II produce the same clinical signs: crystalluria, xanthine stones, and possible kidney failure. Accompanying diseases among humans can include duodenal ulcers, myopathies, and arthropathies.

Xanthinuria occurs in various breeds of dog, but primarily in the Cavalier King Charles Spaniel, where a recessive autosomal heredity has been assumed.[42,43] Various breeds of cat, both male and female, can suffer from xanthinuria, but genetic studies have yet to be performed. Among the submissions to the urinary stone laboratory in Bonn, there were 22 xanthine stones (0.29%) from dogs (see Chapter 2) and 6 from cats (0.33%) (see Chapter 3).[8]

Secondary acquired xanthinuria can occur following treatment with allopurinol or with purine-rich diets.[28,44,45]

Urate stones

In dogs and cats, all of the urate from purine metabolism is metabolized into allantoin and excreted as a well diluted compound in the urine (**9**). Benedict discovered hyperuricosuria in Dalmatians in 1916.[46] This was linked to reduced uricase activity. However, examination of serum and liver samples proved that uricase activity in Dalmatians is similar to that found in other breeds.

The high concentration of uric acid in the serum and urine of Dalmatians (*Table 7*) has been the subject of numerous studies; a variety of uric acid transport defects were found to be responsible:

- Urate transport disorders in the membrane of liver cells.[47]
- Generalized urate transport disorder, i.e. delayed intestinal uptake and reduced reabsorption in the proximal tubule.[48,49]
- Independent carrier-induced urate transport defect in the liver and the kidney.[50]

Table 7 Comparison of uric acid concentrations in the serum and urine of humans, Dalmatians, and dogs other than Dalmatians.[8]

	Human	**Dalmatian**	**Not Dalmatian**
Serum uric acid (mg/100 ml)	3.0–7.0	1.0–2.0	<0.5
Uric acid in the urine (mg/24 hr)	500–700	400–600	10–20

Recent genetic studies in Dalmatians and the cross-breeding of Dalmatians with Pointers, have helped to rule out the implication of *galectin 9* and urate oxidase genes in hyperuricosuria in Dalmatians.[51,52] A marker was located in a genome scan and a linkage analysis of Dalmatian–Pointer crossbreeding. Haplotype analysis in the vicinity of the marker revealed an interval that contains the hyperuricosuria mutation and includes 24 genes.[53] Geneticists hope to establish a link to the loss of uricase for the conversion of uric acid into allantoin, both in Dalmatians and in humans.

Unlike in humans, where uric acid urolithiasis is seen, the excessive uric acid excretion in Dalmatians and other dogs with uric acid transport disorders leads to the formation of uric acid salts or urates. Ammonium urate is normally formed. This necessarily increases ammonium excretion, which is helped by:

- Nonphysiological portal circulation with reduced ureagenesis from ammonia.
- Increased ammonium concentration in the blood.
- Increased renal tubular ammonium secretion.
- High protein intake.
- Low urine pH.
- Low volume of urine.

> As urate stones do not occur in all Dalmatians, the genetic defect that causes high uric acid excretion should be regarded as a predisposition that requires the interplay of several factors for the formation of urinary stones.

Urate stones are also often seen in dogs with congenital portosystemic shunts, a disease that is fairly common in some breeds (e.g. Yorkshire Terrier, Dachshund, Maltese, Irish Wolfhound) and is assumed to be polygenetically inherited. The direct communication between portal and systemic veins leads to reduced blood flow in the liver and consequently reduced liver function, as well as reduced conversion of uric acid into allantoin and of ammonia into urea.

There is no distinct breed disposition in cats for the initial occurrence of urate stones, but Persians and Himalayans have a predisposition for portosystemic shunts. Cats normally excrete high levels of ammonia, which, when combined with high urate excretion, very low urine pH, and low volumes of urine, can lead to the formation of urate stones.

Other genetic defects with a risk of urinary stone formation

In human medicine, the following genetic defects have been identified in association with urinary stone formation:

- Adenine phosphoribosyltransferase (APRT) deficiency leads to the formation of 2.8-dihydroxyadenine, which is relatively insoluble in urine.[54,55]
- Type I primary hyperoxaluria (PH) with alanine glyoxylate aminotranferase (AGT) deficiency and type II PH with glyoxylate reductase (GR) deficiency lead to excessive production of oxalate with high plasma oxalate concentrations and high oxalate excretion in the urine. This results in progressive systemic oxalosis with nephrocalcinosis and urinary stone formation.[56] In dogs and cats, type I PH is not genetically determined. Presumed cases of PH with hyperoxaluria and increased L-glyceric acid in the urine have been described, which corresponds to a type II PH.[57-59] However, increased glyceric acid excretion in the urine alone is insufficient for classification as type II PH.[59,60]
- The high familial frequency of idiopathic calcium oxalate stones suggests a probable genetic link.[61] A gene that is also responsible for absorptive hypercalciuria has been identified.[62]

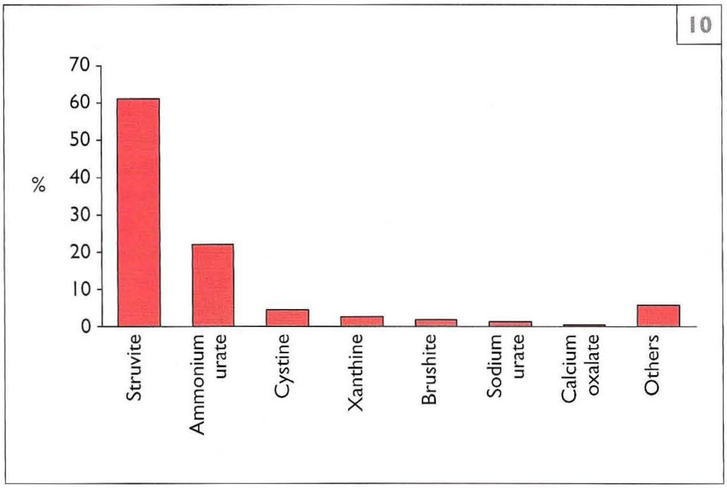
The increase in the frequency of calcium oxalate stones in dogs and cats is a multifactorial event, with the genetic factors probably leading to the high incidence in individual breeds.

Genetically induced urolithiasis is manifest from a very early age. This becomes clear when evaluating the types of urinary stones in dogs in the first year of life (**10**). The frequency of ammonium urate, sodium urate, and xanthine stones is very high at this age; calcium oxalate stones seldom occur at this age. Urinary tract infections with subsequent urinary stone formation are very common in these dogs.

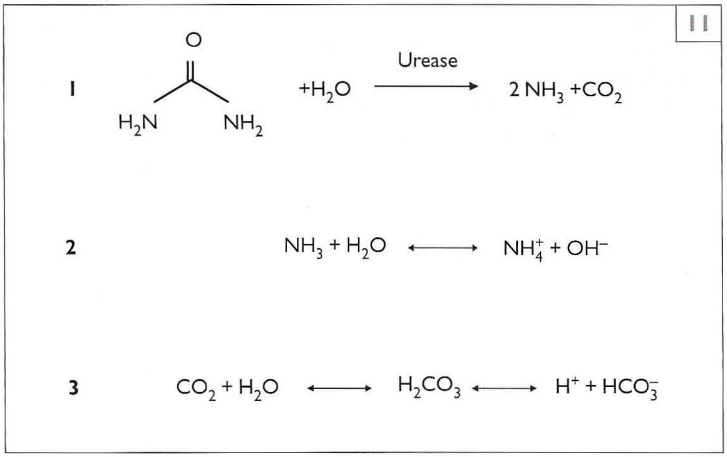
INFECTIOUS CAUSES

Infections with urease-producing bacteria cause urea to be broken down into bicarbonate and

10 Urinary stones in dogs in the first year of life, Germany 1984–2001 (n = 221).[8]



11 Urea split by urease in an aqueous environment.


11
1
O
H_2N
NH_2
$+H_2O$
Urease
$2\,NH_3 + CO_2$
2
$NH_3 + H_2O \longleftrightarrow NH_4^+ + OH^-$
3
$CO_2 + H_2O \longleftrightarrow H_2CO_3 \longleftrightarrow H^+ + HCO_3^-$

ammonium ions. An alkaline urinary environment develops (**11**).

The best-known producers of urease in the dog are *Staphylococcus intermedius* and *Proteus* spp.[63,64] (*Table 8*). Other bacteria that produce urease include *Klebsiella* spp., *Pseudomonas* spp., and *Corynebacterium* spp. In the dog, however, their role in the production of struvite stones is minimal.[65] *Ureaplasma urealyticum* is effective in splitting urea,[3] but has no effect on the animal, except in individual cases, as described.[66]

N.B. Approximately 0–5% of various strains of *Escherichia coli*, *Entercoccus*, and *Pseudomonas aeruginosa* can also produce urease.

Table 8 The most common urease-producing bacteria.

Bacteria that always produce urease (>98%)

Proteus spp.
Providencia rettgeri
Morganella morganii
Corynebacterium urealyticum
Ureaplasma urealyticum

Bacteria that may produce urease

Enterobacter gergoviae
Klebsiella spp.
Providencia stuartii
Serratia marcescens
Staphylococcus spp.

At pH levels >7.0, certain calcium and magnesium phosphates are poorly soluble in urine and result in crystalluria and possible urinary stone formation (**12**).

Magnesium ammonium phosphate hexahydrate (struvite) is classically associated with infections. Occasionally, admixtures of carbonate apatite (calcium phosphate containing carbonate) are found in infection-induced stones that are not a direct result of the infection, but crystallize because of the high urinary pH.

> Stones caused by urinary tract infections mainly consist of pure magnesium ammonium phosphate hexahydrate (struvite).

NUTRITION

In western countries, the consumption of animal protein, fat, purified carbohydrates, and alcohol has increased in humans, whereas there has been a reduction in fibre and calcium intake.[67] The consequences of this dietary change include excess weight, systemic acidosis, and increased urinary excretion of calcium, uric acid, and oxalate, as well as reduced excretion of citrate and magnesium. This has created favourable conditions for the formation of calcium oxalate stones.

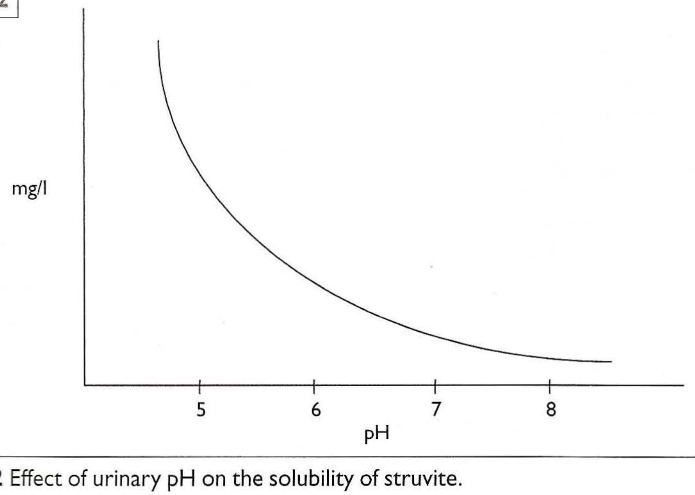
> The increase in urolithiasis among humans in the second half of the twentieth century can be directly associated with the rise in prosperity and dietary changes.

Some studies have clearly demonstrated that a strict diet can normalize the composition of human urine and reduce the incidence of urolithiasis.[68,69]

In the past, urolithiasis was relatively rare in pet animals (dog, cat, rabbit, and guinea pig). However, changes in living conditions to a more urban-style environment with reduced space, lack of exercise, neutering, rich food intake (especially dry food), and a higher life expectancy, have increased the incidence of urolithiasis. Almost two thirds of the dogs with urinary stones that were studied were over 5 years old, and 35–45% were obese; excess bodyweight lowers resistance to infections. Almost 60% of the animals with urinary stones in one European study presented with evidence of urinary tract infection,[8] which can lead to the formation of alkaline urine.

> A reduced fluid intake, which is partially associated with a dry diet, may cause the urine's specific gravity and pH to increase, creating favourable conditions for phosphate crystallization.

12



12 Effect of urinary pH on the solubility of struvite.

Of all the urinary stones in dogs studied in the period 1980–1984, 95% were struvite (55%) or genetically derived stone types (e.g. cystine, 22.5%; ammonium urate, 7.5%). Only 5% were calcium oxalate stones.[34]

Similar results were reported in the USA in the same period: struvite stones were in the majority at 78% (1981) and 60% (1984).[28] Stone-dissolving diets were therefore conceived for struvite, with reduced quantities of protein, magnesium, and phosphate, and increased sodium chloride to stimulate fluid intake. Successful use was even made of diets designed to acidify the urine to dissolve struvite stones. However, urine-acidifying diets are not suitable for long-term use in animals with concurrent disease such as high blood pressure, heart disease, or nephrotic syndrome. The uncontrolled use of some diets can also contribute to the formation of calcium oxalate stones.

A recent study in dogs with urolithiasis and healthy dogs, using a multivariate analysis, has proved that there is an increased risk of calcium oxalate stone formation with dry diets with a low sodium and other electrolyte content (phosphorus, calcium, magnesium, potassium, and chloride) in comparison with a sodium-rich food.[70] According to this study, even diets with a high urine-acidifying potential and low moisture and fibre content are associated with an increase in calcium oxalate stone formation.

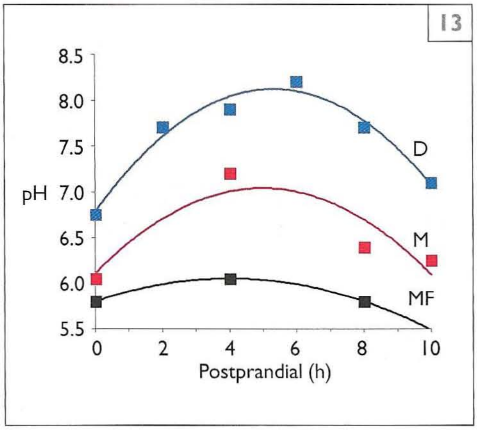
Stevenson et al. demonstrated that the addition of sodium chloride to dry food decreased the risk of calcium oxalate lithiasis in healthy Miniature Schnauzers and Labrador Retrievers.[71] However, the addition of sodium chloride to moist food had a significant effect on the relative supersaturation of the urine with calcium oxalate in the Miniature Schnauzer alone.

All of these studies show that the diet can be used to dissolve urolithiasis in the dog but that it is also of crucial importance in prevention and treatment.

Nutrition also plays a significant role in the pathophysiology and treatment of urolithiasis in cats. In some studies in the 1970s, an almost ten-fold increase in dietary magnesium intake caused the formation of struvite stones and subsequent urinary tract obstructions.[72] Subsequent studies have shown that with a comparable magnesium content but an acidic urine pH (about 6.0), struvite stones can be dissolved,[73] i.e. magnesium is only a relevant factor if the pH level in the urine is not controlled.[74] When feeding commercial moist and dry food to cats in the past, a strong postprandial increase in urine pH to >8.0 has been observed (**13**).[17,75,76]

In a comparison between low- and high-protein diets for cats, a positive correlation was found between protein intake and specific gravity, as well as urea, creatinine, and ammonium excretion in the urine. Struvite crystalluria was always increased with a protein-rich diet.[77]

The discovery of the link between nutrition and lithiasis in cats has resulted in the development of ready-made diets, which has helped to reduce magnesium excretion and increase urine acidification. Compounds used for urine acidification have included ammonium chloride, ascorbic acid, and methionine. It has therefore become possible to prevent and even dissolve struvite stones. It is also important to remember that, as with dogs, this food should only be used in the long term under veterinary supervision. The tendency for certain ready-made diets to acidify the urine has been thought to be responsible for the rise in calcium oxalate urolithiasis in the 1990s.[27,78] In



13 Postprandial changes in urine pH under various feeding conditions (modified after Buffington in 1985, Lewis in 1984, and Kienzle in 1993).[17,75,76] (D = dry food; M = moist food; MF = moist food with L-methionine) addition, urine-saturating diets with reduced magnesium and potassium content can induce hypokalaemia and chronic kidney failure.[79] In humans, acidifying diets have been associated with impaired bone metabolism and increased urinary calcium excretion.[80,81]

> Unlike dogs and humans, in whom struvite stones are primarily the result of urinary tract infections with urease-producing bacteria, dietary factors have a greater impact in cats. The low prevalence of urolithiasis in cats of 1–2% does not justify the systematic use of urine-acidifying diets. Indeed, such diets are contraindicated with calcium oxalate stones and in cases of idiopathic FLUTD.[82] Determination of the relative supersaturation (RSS) can help to develop diets that act as a combined struvite and calcium oxalate stone prophylaxis.

STRESS

Epidemiological studies in Germany have shown that urinary stones in humans are usually diagnosed between the ages of 25 and 50 years (see **2**), i.e. at a period of life when stress is common with the demands of work and family. Unpublished reports have demonstrated a marked increase in the incidence of urinary stones in air force pilots. In stressful situations, the increased production of adrenocorticotrophic hormone (ACTH) raises levels of adrenaline and cortisol and inhibits prostaglandins. Renal calcium excretion is also increased via the stimulation of parathyroid hormone production.[83,84] Stress causes metabolic acidosis, which can predispose the animal to the formation of urinary stones and especially calcium oxalate. Under stressful conditions, there is usually an increase in fluid loss through the skin. Increased vasopressin production promotes the absorption of water in the kidneys, resulting in highly concentrated, hypertonic urine. Experiments with dogs subjected to psychological stress have demonstrated that urinary osmolality significantly increases and urine volume decreases.[83] This is associated with the concentration of substances that are usually excreted via the urine, and an increased potential for urinary stone formation.

Even under the stress of low temperatures, calcium excretion increases markedly. In astronauts, calcium excretion is increased by immobilization and stress.[84]

The importance of various environmental factors can be seen in cats with urolithiasis. There was a report of one cat whose urinary pH of 6.1, under normal domestic conditions, increased to 7.6 while in transit to the clinic.[82] When other causes of a pH increase, such as diet, urinary tract infection, or renal tubular acidosis can be ruled out, stress should be considered.[85]

Theories on the crystallization of urinary components

NUCLEATION, GROWTH, AND AGGREGATION

The solubility product is defined as the dissolution of a substance in water at a certain temperature, e.g. 20°C. In complex solutions such as urine, there are interactions with other constituent substances that may promote (promoters) or suppress crystallization (inhibitors). The pH value plays a crucial role in initiating the crystallization of some substances. Thus, once the solubility product has been exceeded, a substance-specific metastable concentration zone is formed (**14**); this may be wide or narrow.

> The crystallization of a substance out of a solution can only occur if a certain concentration, known as its solubility product, is exceeded (supersaturation of the urine).

It is only when the concentration of the substance to be crystallized exceeds the formation product (saturation) that crystallization necessarily takes place.

Crystallization begins with the formation of the smallest crystals (nucleation), which can also attach themselves to alien crystals or alien surfaces. Spontaneous crystallization in a solution free from foreign bodies is described as homogeneous nucleation. Heterogeneous nucleation occurs in the presence of alien crystals, highly molecular substances, or alien surfaces. Then it proceeds from a oversaturated solution to the growth and the aggregation of the crystals. Microliths are formed, which can be the preliminary stages of urinary stones.

Crystalluria is actually a normal physiological and necessary physical and chemical process that reduces urinary supersaturation. With sufficient diuresis, small crystals are flushed out of the urinary tract. If the microliths exceed a certain size, they can become lodged in the renal calyces, ureters, or bladder where they continue to grow into urinary stones. Urinary stones can also arise from fixed microliths, e.g. in the renal papillae or in necrotic tissue, if there is permanent supersaturation of the urine with stone-producing substances.

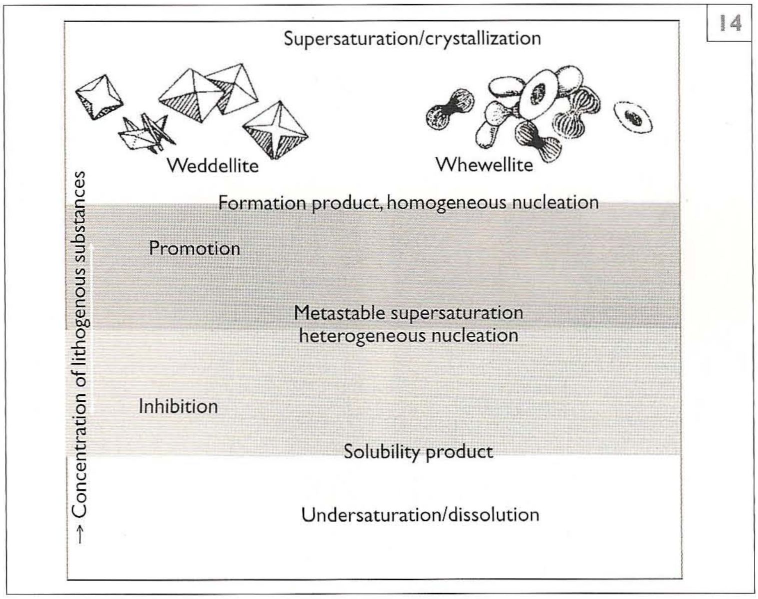
THEORIES ON STONE FORMATION IN URINE

Three theories have been proposed to explain the different mechanisms behind the formation of the various stone types in the urine:

- The supersaturation theory.
- The matrix theory.
- The inhibitor theory.

With homogeneous nucleation, the process described above corresponds to a pure *supersaturation theory*, where the solubility product and formation product are exceeded. The matrix and inhibitor theories consider whether there is a large or small metastable zone in the specific conditions (**14**).

Almost all urinary stones contain small quantities of macromolecular substances, such as mucoproteins, which also can have calcium-binding properties. This has led to the *matrix theory*, i.e. the theory that the macromolecular substances were not included in the urinary stone by chance, but form a framework for taking up and storing the stone substance. This theory is particularly plausible in the case of infection-induced stones with bacterial inclusions or urethral plugs. Foreign bodies such as plant material or splinters of wood are regularly found forming the cores of urinary stones.[86,87] Unusual materials include pine needles in struvite stones[88] or even a sewing needle that entered the bladder as a wandering foreign body via the gastrointestinal tract.[89] The commonest foreign body that is found as a core in urinary stones is surgical suture material from previous cystotomies.[88]


14
Supersaturation/crystallization
Weddellite
Whewellite
Formation product, homogeneous nucleation
Promotion
Metastable supersaturation
heterogeneous nucleation
Inhibition
Solubility product
Undersaturation/dissolution
→ Concentration of lithogenous substances

14 Diagram of crystal formation in urine as a function of concentration (example of crystal: calcium oxalate).

The storage of organic macromolecular substances is shown in **15** in a cross-section of a calcium oxalate stone. The well formed tips of weddellite crystals that have been converted internally into fine-grained whewellite through crystal anhydration can be seen in polarized light in **15a**. Following the almost complete demineralization of the thin section in a cuvette with an EDTA solution, only the macromolecular matrix substance remains behind (**15b**).

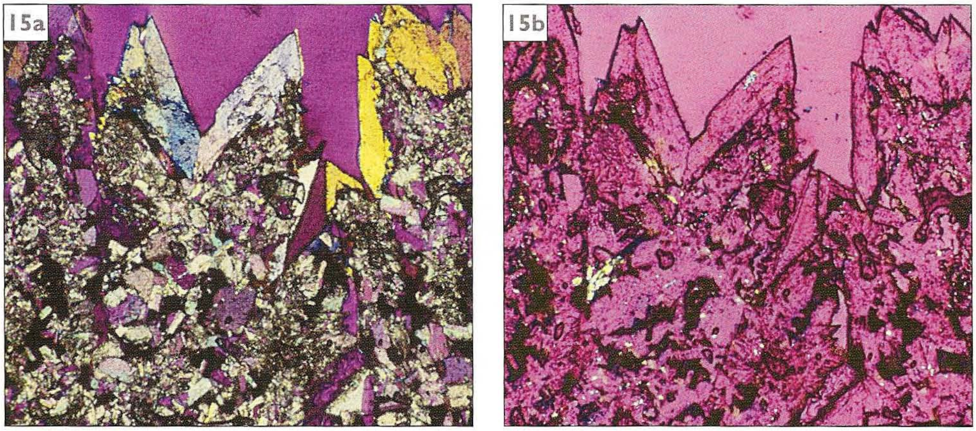
The *inhibitor theory* is particularly plausible for the formation of calcium oxalate stones; it also provides practical treatment solutions. For example, at high concentrations of the inhibitors (citrate, magnesium, or glycosaminoglycan), along with a weakly acidic urine pH, crystallization slows down. In **14**, the metastable zone would then be very wide or the solubility product would not even be attained. If the inhibitors are weak and the promoters for calcium oxalate (oxalate, calcium, urate) are present in high concentrations, the formation product is rapidly exceeded and crystallization takes place.

The above theories can only be used to explain and reproduce the formation of urinary stones to a limited extent; in conclusion, a combination of the following factors is responsible for urolithiasis:

- Sufficiently high concentration of urinary stone-producing substances.
- Sufficiently slow passage through the urinary tract.
- Urine pH that favours crystallization (struvite, urate).
- Crystallization core.
- Lack of inhibitors of crystallization and stone formation.

MODELS FOR CALCULATING SUPERSATURATION

The precipitation of a stone-producing salt is determined by its degree of supersaturation in the urine. Owing to the multitude of ionic compounds in the urine, there are some highly complex interactions, i.e. numerous ions compete with each other in the formation of sparingly soluble salts or highly soluble complexes. Robertson *et al*. mapped the impact of the activity product on urolithiasis.[90]



15 (**a**) Thin section of a calcium oxalate stone from the bladder of a dog. This view is in polarized light with crossed polarizers. The pointed weddellite crystals are converted internally into fine crystalline whewellite; since the weddellite crystals retain their external shape, the process is known as pseudomorphism. (**b**) Once the crystalline components have been dissolved, the enclosed organic components remain behind, retaining their crystal shapes.

EQUIL

Of all known solubility products and complex formation constants, credit should be given to Bird Finlayson for developing a computer program that calculates the RSS of urinary stone substances.[91] In its subsequently developed form, EQUIL 2, this EQUIL program is still the 'gold standard'[92] in human medicine for calculating the relative supersaturation of stone-producing substances in the urine. Using the easily identifiable analytical parameters affecting urolithiasis – pH, sodium, potassium, ammonium, calcium, magnesium, chloride, sulphate, phosphate, citrate, oxalate, uric acid, and creatinine – as control parameters, the RSS for the formation of struvite, calcium oxalate, calcium phosphate, and brushite can be determined with this program. The high analytical expenditure makes this program unsuitable for routine studies, but it is extremely helpful in resolving scientific problems. The EQUIL program was adapted to the urinary composition of dogs and cats for the development of new prescription diets for the treatment of urolithiasis.[93,94]

SUPERSAT

The SUPERSAT program was developed by Robertson and adapted for use in veterinary medicine. Like the EQUIL program, it facilitates the calculation of the RSS for various urinary stone substances.[90,95] The total concentrations of 12 urinary parameters and urine pH are required to calculate the RSS as a measure of the risk of urinary stone formation. When comparing the EQUIL and SUPERSAT programs for human and dog and cat urine, it was established that a significant overestimation for RSS had been calculated with the EQUIL program, especially for struvite. The RSSs calculated by both programs for calcium oxalate are only slightly different.[94,95] Owing to the relatively high cost, the use of these programs is restricted to special clinics and research facilities. The EQUIL program and more particularly the SUPERSAT program are now used to develop new diets for the prevention and treatment of urolithiasis in dogs and cats.

Activity product indices

The calculation of the activity products (APs) is a simplified way of determining the risk of urolithiasis.[96,97] A few urinary analyses are all that are required. The calculation formulae can be programmed into a computer.

Example 1:

AP index (struvite)

$$= \frac{D \times Mg^{1.06} \times NH_4^{\,0.98} \times PO_4^{\,0.71} \times (pH - 4.5)^{6.3}}{\text{urinary volume}^{\,2.3}}$$

D: factor for the collection period: 8 hr = 5.64×10^{-4}
24 hr = 3.80×10^{-4}

Example 2:

AP index (calcium oxalate)

$$= \frac{A \times Ca^{0.84} \times \text{oxalate}}{\text{citrate}^{\,0.22} \times Mg^{\,0.12} \times \text{volume}^{\,1.03}}$$

A: factor for the collection period: 8 hr = 3.2
24 hr = 1.9

BONN risk index

The EQUIL and AP index calculation models can only provide an approximation of the actual status, as in most cases ionic and nonionic macromolecular substances dissolved in the urine are not taken into account.

A model has been developed to determine the risk of calcium oxalate urolithiasis, whereby crystallization is triggered directly in the native urine.[98,99] The BONN risk rndex (BRI) is calculated from the initial concentration of ionized calcium using ammonium oxalate until the initiation of calcium oxalate crystallization in the urinary specimen:

$$BRI = [Ca^{2+}] / (Ox^{2-})$$

The risk potential is read on a curve (**16**):

BRI >1/l increased risk; BRI <1/l reduced risk

A commercially available device (Urolizer®, Raumedic, D-95205 Münchberg) is used for the routine calculation of the BRI in human medicine. To date, there have been no reports of its use in the veterinary sector or of its reliability.

Urinary stone analysis

INTRODUCTION

The treatment and prevention of recurrent urolithiasis are specific to the composition of the stone. Accordingly, the most important diagnostic test following the removal of a urinary stone is a qualitatively and quantitatively precise urinary stone analysis. The results of the analysis should include all chemical components of the stone using at least 5% of its weight.

CHEMICAL ANALYSIS

The methods of urinary stone analysis that were commonly performed in the past, using standard commercial kits, should be regarded as outdated. These kits require the dilution of the urinary stone substance, which destroys the structure of the stone and important types of stone are not identified. A quality control study into the reliability of the chemical analysis of urinary stones revealed false results in over 50% of cases;[100] these methods are therefore now considered to be obsolete.[3,101]

MICROSCOPIC EXAMINATION

Urinary stones are primarily crystalline in nature with a characteristic light refraction pattern that can be analysed under the microscope using immersion fluids. Phase contrast or polarization microscopy is a reliable means of identifying individual crystal structures (**17**).

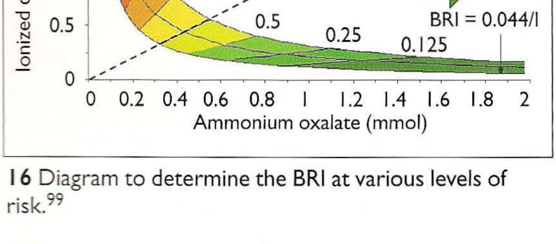
The microscopic examination of granular preparations can give very accurate results. However, it requires special training and its use is therefore restricted to qualified individuals. There are no documented, controllable, objective measurement details; such details are also lacking for the other analytical methods described below.

SCANNING ELECTRON MICROSCOPY

Scanning electron microscopy is a special method for the micromorphological examination of surfaces. It produces highly detailed images, enabling the accurate description of the surfaces and cut surfaces of objects, and any changes thereto caused by external influences. The characteristic x-rays created by this method can also be used for elemental analysis. It is therefore possible to analyse the morphology and composition of crystals. Scanning electron microscopic images of human and animal urinary stones have been used to characterize the phase structure and its conversion forms.[33,102-108]

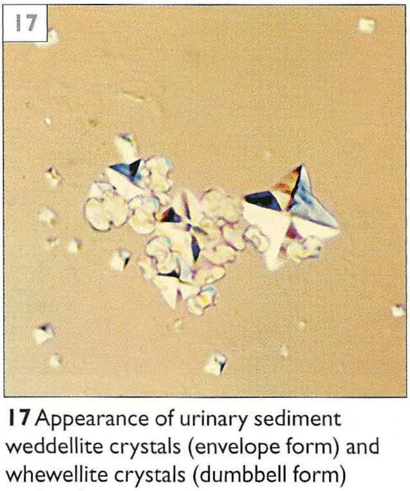
18 shows scanning electron microscope pictures of urinary sediment crystals, and the surfaces and broken surfaces of various urinary stones in animals.

16

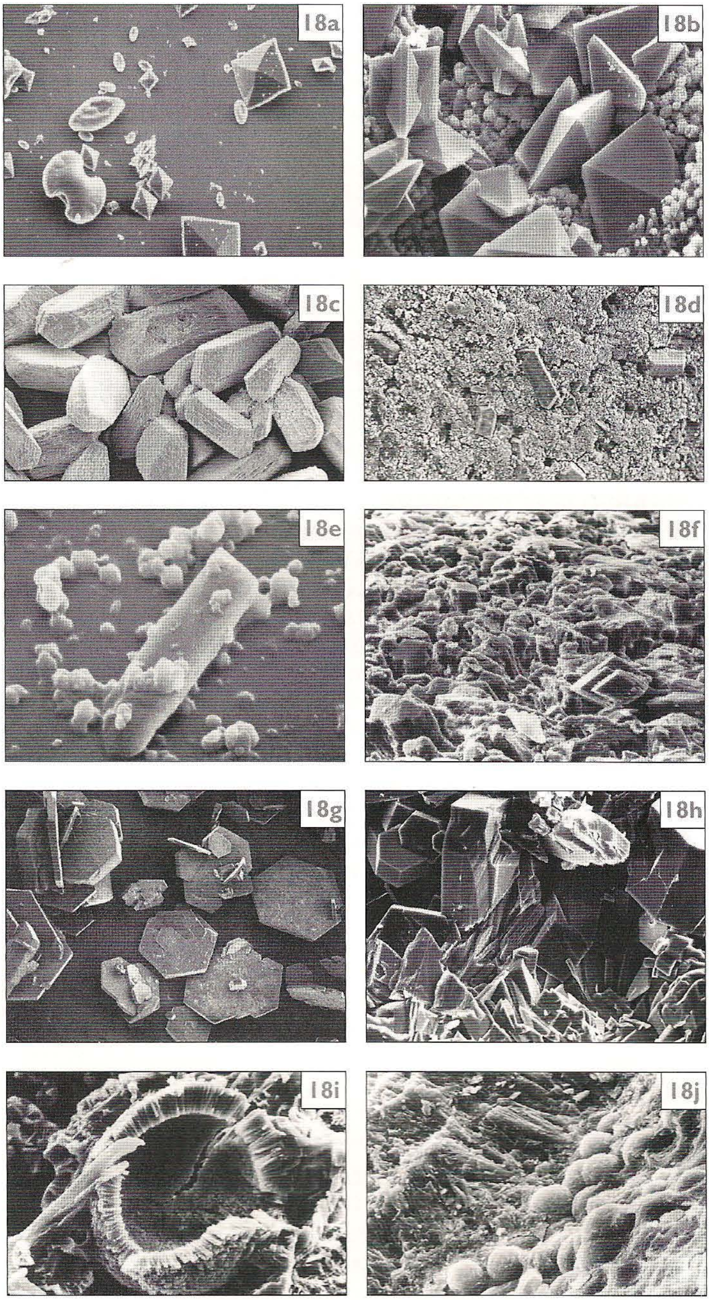


16 Diagram to determine the BRI at various levels of risk.[99]

17



17 Appearance of urinary sediment weddellite crystals (envelope form) and whewellite crystals (dumbbell form) under phase-contrast microscopy.



18 Scanning electron microscopic pictures of urinary crystals and urinary stones. (**a**) Calcium oxalate urinary crystals, bipyramidal weddellite crystals, whewellite crystals with dumbbell and ellipsoid shapes. (**b**) Broken surface of a urinary stone in a rabbit, bipyramidal deformed weddellite crystals and pseudoamorphous spherical calcium phosphate groups; infrared spectrometric analysis: 55% calcite, 35% weddellite, 10% amorphous calcium phosphate. (**c**) Struvite urinary crystals, coffin-shaped. (**d**) Surface of a urinary stone in a dog (Beagle), compact, coffin-lid-shaped struvite crystals, beside and above fine crystalline carbonate apatite. (**e**) Brushite urinary crystal, basalt columnar, fine crystalline carbonate apatite. (**f**) Surface of a urinary stone from a dog (crossbreed), coarse crystalline, basalt columnar brushite crystals; infrared spectrometric analysis: 100% brushite. (**g**) Cystine urinary crystals, characteristic hexagonal crystals. (**h**) Broken surface of a urinary stone from a cat, hexagonal crystals with prismatic and planar configurations; infrared spectrometric analysis: 100% cystine. (**i**) Broken surface of a urinary stone from a dog (Dalmatian), large crystal of spherical external shape, individual crystals on the inside, arranged in parallel rows; infrared spectrometric analysis: 100% monoammonium urate. (**j**) Surface of a urinary stone from a dog (Dachshund), radial beam and spherical structures; infrared spectrometric analysis: 100% xanthine.

X-RAY DIFFRACTION

The distinctive crystalline structures of urinary stones produce characteristic monochromatic x-ray diffraction patterns, as a function of the type of crystal lattice (**19**). The diffraction patterns are drawn and compared with test diagrams to give an accurate qualitative and semi-quantitative analysis.[109]

Amorphous and pseudoamorphous substances such as proteins, other matrix connections, and fine crystalline calcium phosphate produce little or no x-ray diffraction and cannot be analysed by this method.

X-ray diffraction is a very precise method of urinary stone analysis; however, it is very costly and requires special protective measures.

INFRARED SPECTROMETRY

Infrared spectrometry is used to examine the chemical structure of a substance. This method is also referred to as molecular spectroscopy. The principle is based on the fact that all chemical molecules are excited to a different extent by infrared light, as a function of their spatial structure and the relationships of the atoms to the oscillations. Accordingly, energy from the infrared irradiation is selectively absorbed. The resultant absorption spectrum is characteristic for each molecule, and is also referred to as the 'fingerprint' of a substance. The distinctive structures of the various types of urinary stones produce different infrared spectra (**20**). Mixed substances can also be confidently analysed using this method.[110]

Today, infrared spectrometry is the method of choice for the analysis of urinary stones. In the author's laboratory (Hesse), this method has been used since 1980 for the analysis of urinary stones in animals. In 2006, the laboratory was equipped with the latest highly sensitive device (a Fourier Transform infrared spectroscopy (FT-IR) spectrometer with attenuated total reflection (ATR) technology). *Table 9* summarizes the infrared spectrometry results of urinary stones taken from dogs from various European countries.

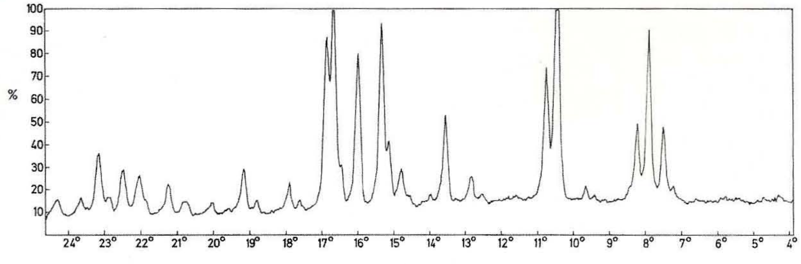
SPECIMEN PREPARATION AND DISPATCH FOR STONE ANALYSIS

Arrangements should always be made for the immediate analysis of urinary stones after removal (whether spontaneous, instrumental, or surgical).

The stones do not require any form of treatment; they should simply be rinsed with water. They should be dried at room temperature or at a maximum of 37°C, as urinary stone substances change at higher temperatures. All types of stone can, however, be sent to the laboratory whilst still damp – the results will not be affected.

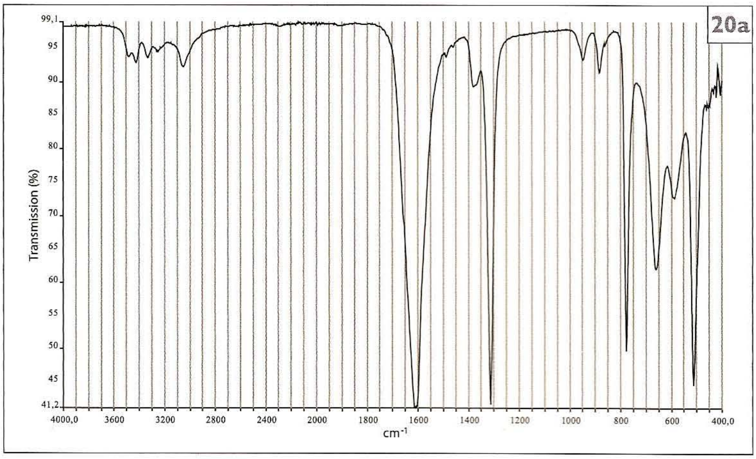
Unbreakable containers or plastic bags and strong envelopes should be used for dispatch. Packaging material can also be obtained from each specialist laboratory.

19



19 X-ray diffraction pattern of struvite.

20 (**a**) Infrared spectrum of a whewellite urinary stone. (**b**) Infrared spectrum of a cystine stone.



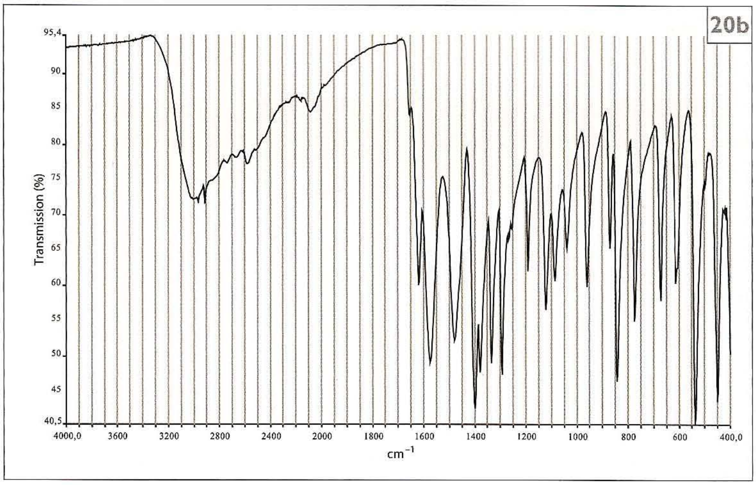
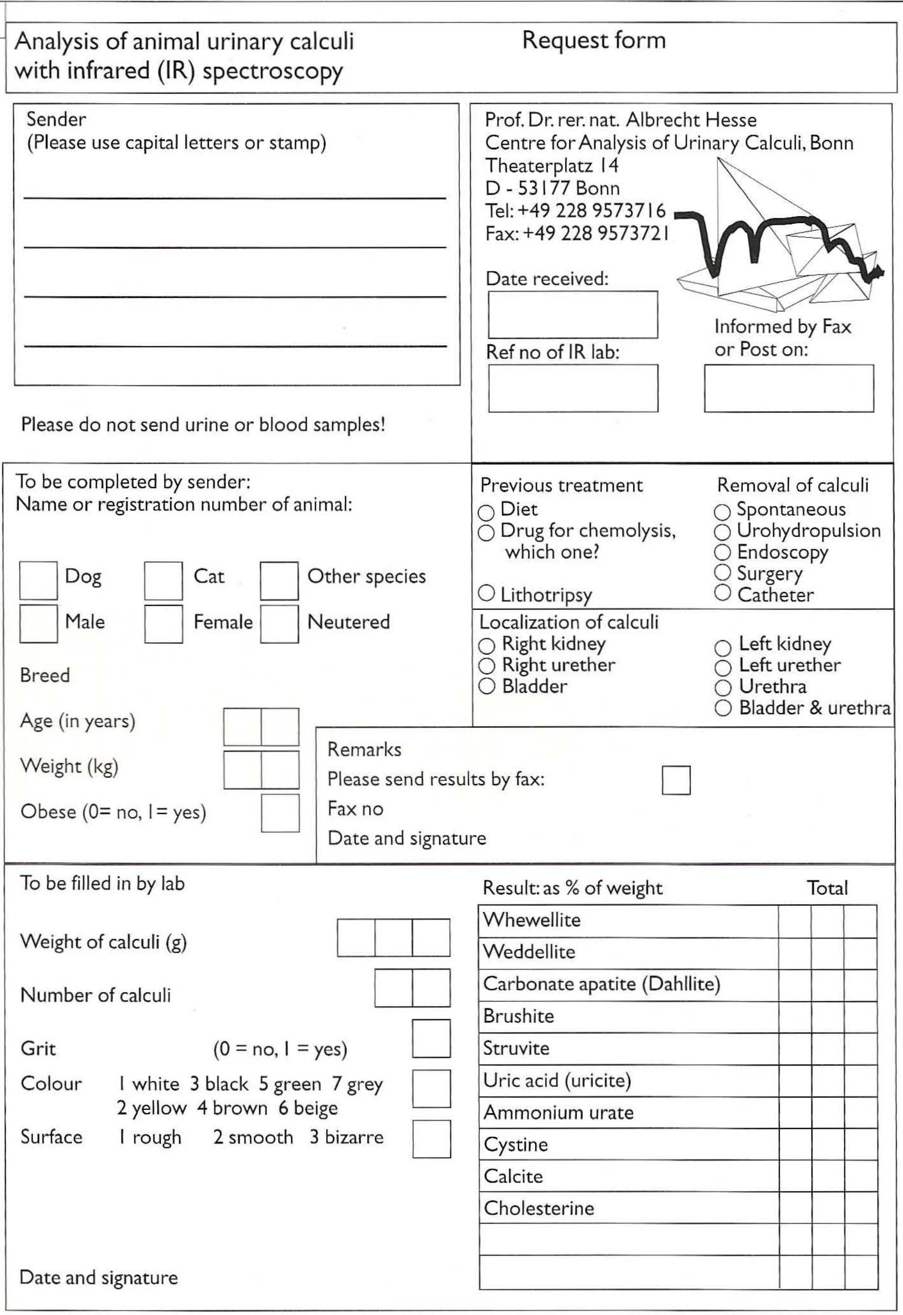


Table 9 Summary of infrared spectrometry results of urinary stones taken from dogs from various European countries.[111]

Country	**Stone count (n)**	**Stone types**				
		Struvite	Weddellite	Whewellite	Cystine	Ammonium urate
Germany	7,633	58.6	8.3	5.4	15.4	6.3
Netherlands	1,335	59.2	20.7	11.2	2.6	3.1
Italy	276	40.6	21.4	19.2	7.3	6.9
Finland	190	34.2	40.0	17.9	1.6	2.1
France	168	49.4	19.6	15.5	4.8	4.1
Switzerland	78	37.2	33.3	11.5	7.7	2.6
Great Britain	74	54.1	17.6	12.2	0.0	8.1
Belgium	63	52.4	22.2	9.5	3.2	9.5
Austria	61	70.5	6.6	6.6	8.2	1.6
Norway	58	53.5	24.1	17.2	0.0	3.5

21



Analysis of animal urinary calculi with infrared (IR) spectroscopy

Request form

Sender
(Please use capital letters or stamp)

____
____
____
____

Please do not send urine or blood samples!

Prof. Dr. rer. nat. Albrecht Hesse
Centre for Analysis of Urinary Calculi, Bonn
Theaterplatz 14
D - 53177 Bonn
Tel: +49 228 9573716
Fax: +49 228 9573721

Date received: ☐

Ref no of IR lab: ☐

Informed by Fax or Post on: ☐

To be completed by sender:
Name or registration number of animal:

☐ Dog ☐ Cat ☐ Other species
☐ Male ☐ Female ☐ Neutered

Breed

Age (in years) ☐☐

Weight (kg) ☐☐

Obese (0= no, 1= yes) ☐

Previous treatment
- ○ Diet
- ○ Drug for chemolysis, which one?
- ○ Lithotripsy

Removal of calculi
- ○ Spontaneous
- ○ Urohydropulsion
- ○ Endoscopy
- ○ Surgery
- ○ Catheter

Localization of calculi
- ○ Right kidney
- ○ Right urether
- ○ Bladder
- ○ Left kidney
- ○ Left urether
- ○ Urethra
- ○ Bladder & urethra

Remarks
Please send results by fax: ☐
Fax no
Date and signature

To be filled in by lab

Weight of calculi (g) ☐☐☐

Number of calculi ☐☐

Grit (0 = no, 1 = yes) ☐

Colour 1 white 3 black 5 green 7 grey
2 yellow 4 brown 6 beige ☐

Surface 1 rough 2 smooth 3 bizarre ☐

Date and signature

Result: as % of weight	Total		
Whewellite			
Weddellite			
Carbonate apatite (Dahllite)			
Brushite			
Struvite			
Uric acid (uricite)			
Ammonium urate			
Cystine			
Calcite			
Cholesterine			

21 Example of a stone analysis request form from the author's laboratory (Hesse).

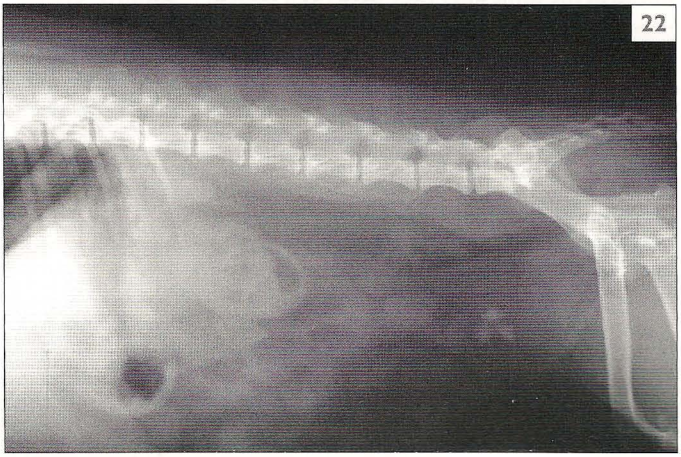
Ideally, all requests for analysis should be sent using an official laboratory form (**21**); the following details should always be provided:

- Species (dog, cat, rabbit, guinea pig).
- Breed.
- Sex (male, neutered male, female, neutered female).
- Age (in months for young animals).
- Weight of animal.
- Overweight? (yes/no).
- Location of urinary stone(s) (left/right kidney, left/right ureter, bladder, urethra).
- Previous treatment: diet (which?), drugs for chemolysis (which?), lithotripsy.
- Method of stone removal (spontaneous, urohydropropulsion, endoscopy, surgery, catheterization).

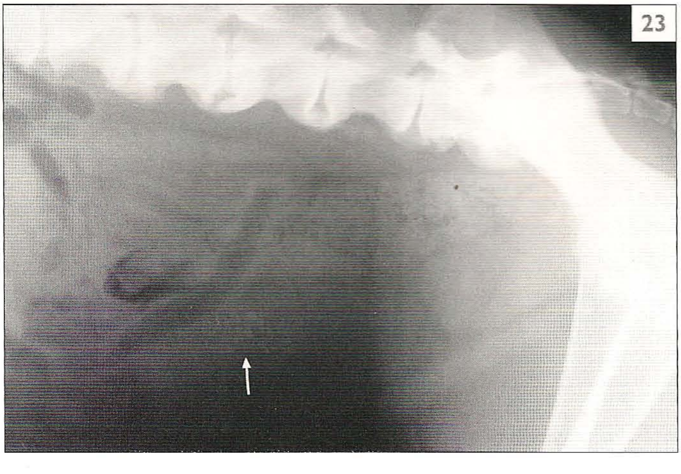
General clinical diagnosis and treatment of urinary stones

CLINICAL SIGNS

The signs of urolithiasis are primarily related to the location of the stones and can vary from symptom-free to an acute emergency. Other determining factors for the clinical presentation are the duration of the disease, and the size and shape of the uroliths. Renal calculi (kidney stones) in dogs and cats are often discovered fortuitously on abdominal radiographs or during an ultrasound examination (**22, 23**). Signs include haematuria, abdominal pain, and nonspecific signs such as anorexia and lethargy. On rare occasions, renal calculi may cause



22 Three irregularly shaped bladder stones in an 11-year-old crossbreed that was radiographed for nonspecific vomiting symptoms. The stones were not removed, as the dog had no lower urinary tract symptoms.



23 Numerous small bladder stones (arrow) barely visible on a radiograph of a 7-year-old male dog with constipation and a palpably large prostate. The radiograph confirms an enlarged prostate, and ultrasound examination was suggestive of benign prostatic hyperplasia. The bladder stones were not removed.

significant renomegaly caused by hydronephrosis. Renomegaly can usually be detected by palpation. If urinary outflow is impeded and renal function is impaired, then signs of renal failure will be present, which usually have a chronic progression. Urinary stones in the ureters can cause the same signs as renal calculi, but they are more commonly associated with renal congestion.

With bladder stones but no obstruction, the classic signs of cystitis are present, such as pollakiuria (frequent voiding of small quantities of urine), dysuria (difficult urination), stranguria (painful urination), and haematuria (discharge of bloody urine). In cases with a concomitant urinary tract infection, the urine is sometimes also cloudy and foul smelling. In rare cases affected animals are asymptomatic and owners notice one or more small urinary stones in the urine after they have been passed.

> The clinical signs of bladder and urethral stones depend on whether there is a urinary obstruction or not.

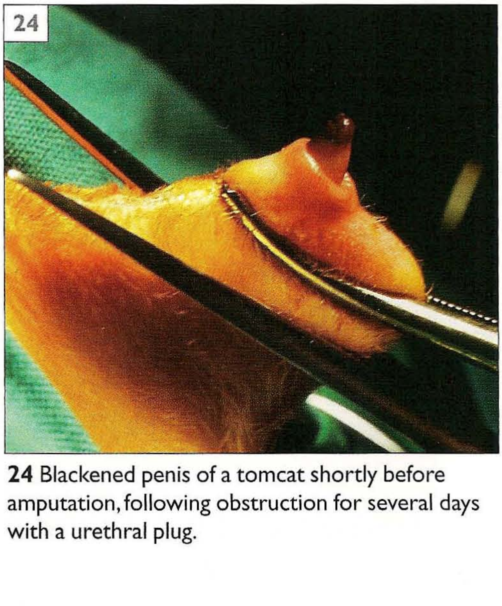
Complete obstruction of the urinary tract with urinary stones results in postrenal azotaemia, which worsens over time due to urinary stasis. As potassium is no longer excreted correctly, hyperkalaemia can ensue, followed by bradycardia. Animals initially make unsuccessful attempts to pass urine, sometimes vocalizing loudly in the process; cats often spend long periods in the litter tray, passing a few drops of blood instead of urine. After a relatively short time (2–3 days), animals become lethargic, anorexic, and, in advanced cases, are presented in lateral recumbency. An extremely full, painful bladder can be found on abdominal palpation and, in the male animal, the penis can be reddened, oedematous, and even partially blackened (**24**). In some cases, urethral stones can be felt; it is particularly important to perform a rectal palpation of the pelvic portion of the urethra in dogs to exclude any other possible diagnoses. In the tomcat, plugs can sometimes be seen and felt at the tip of the penis (**25**).

Urinary stones are often secondary to another disease, e.g. calcium oxalate stones caused by hypercalcaemia or in connection with hyperadrenocorticism, or urate stones in animals with a portosystemic shunt; clinical signs are principally related to the primary disease.

DIFFERENTIAL DIAGNOSIS

Although urolithiasis is a very frequent cause of the aforementioned clinical signs, such as haematuria or dysuria, and various breeds are

24



24 Blackened penis of a tomcat shortly before amputation, following obstruction for several days with a urethral plug.

predisposed to urinary stones (*Table 2*, p. 11), a differential diagnosis should always be made.

The surface of enlarged kidneys, whether uni- or bilateral, should be carefully assessed. An uneven surface is not characteristic of renal calculi, but is more indicative of cysts, tumours or haematomas. With a smooth surface, the differential diagnoses include compensatory hypertrophy, generalized inflammation (e.g. leptospirosis in the dog or feline infectious peritonitis (FIP) in the cat), tumours (e.g. lymphoma), or hydronephrosis.

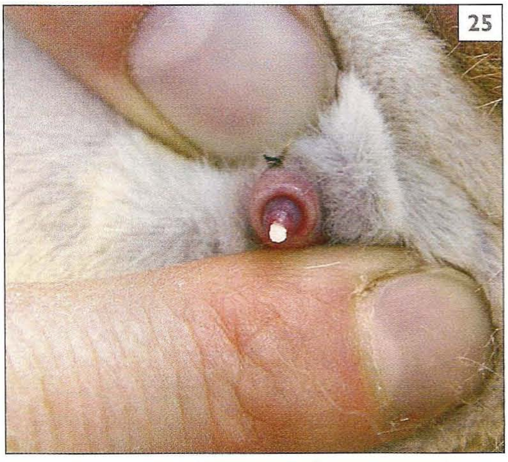
Urinalysis should be used to confirm that haematuria is the cause of red urine, and not haemoglobinuria or the presence of any other colouring agents. If haematuria is present throughout urination, an upper urinary tract disorder (cysts, renal infarction, renal tumour, or trauma) or systemic disease such as a coagulation disorder should be considered as differential diagnoses. If signs occur mainly at the start of micturition, disorders of the urethra (granuloma, tumour) or prostate (male animal) should be considered as differential diagnosis. If lower urinary tract signs are observed, bacterial cystitis, a bladder tumour, or prostate disorder should be considered. In cats, however, idiopathic FLUTD is the most common cause of haematuria, dysuria, and stranguria, but other causes should always be excluded first.

> With haematuria, the location of the haemorrhage can sometimes be determined by the phase at which the blood appears during micturition.

GENERAL DIAGNOSTIC CONSIDERATIONS

In animals with clinical signs of urinary tract disorders, a detailed *history* should always be taken. The following questions should be put to the owner:

- Is this the first episode or has the animal had urinary tract problems previously?
- Is there any history of disease in animals from the same litter or in other related animals?
- Does the animal have another known ailment?
- What does the animal eat (precise feed history)?
- Is the animal currently taking any medications (type and quantity)?
- At what point during urination is blood observed?
- Does the animal exhibit any pain, and is any urine passed at all?



25 Plugs at the tip of the penis of a tomcat with a urinary tract obstruction.

During the *clinical examination*, a careful abdominal palpation is essential. Bladder stones can sometimes be palpated. Rectal palpation is indicated in both male and female dogs, and stones or other changes can sometimes be felt in the urethra.

In the event of a urinary tract obstruction, animals are often in a poor general condition (lateral recumbency, bradycardia, and shock) and intravenous fluid therapy with a balanced electrolyte solution is indicated. The next step is to attempt catheterization (if possible without anaesthesia or sedation). If there are no intraluminal (urinary stone) or intramural (tumour, granuloma) obstructions, this should be possible. Urinary stones can sometimes be flushed back into the bladder (see page 50). The bladder should then be completely emptied, keeping a sterile sample for analysis.

> A complete urinary tract obstruction is always an absolute emergency!

Even if there is no obstruction of the urinary tract, catheterization is indicated, especially in the event of stranguria or pollakiuria. Small concretions in the urethra are easy to feel, and the experienced clinician can sense whether the catheter can be pushed normally into the bladder. The utmost care must be taken to ensure that the catheter is not pushed in too far, otherwise a knot can form in the catheter inside the bladder (**26**).

Laboratory

> In addition to complete urinalysis including sediment analysis and a complete blood work-up, all cases of serious or recurrent urinary tract disease that are not self-limiting should undergo diagnostic imaging (radiography, ultrasonography) of the urogenital tract.

Urinalysis

Complete urinalysis includes the determination of specific gravity, dipstick analysis, sediment and bacteriological examination with antibiotic sensitivity testing. Wherever possible, the urine should be collected by cystocentesis. Midstream urine or urine collected by catheter can also be examined, but the results need to be interpreted accordingly (see *Table 12*). In some cases, a comparative examination of midstream urine and urine withdrawn by cystocentesis can be revealing. Prior to the examination, the urine must be warmed to room temperature and mixed well. It is very important that urine stabilizers are not added prior to urinalysis – they are only necessary to suppress bacterial growth during transit to the laboratory.

> Urine should always be examined within 30 minutes of collection; otherwise, it should be kept in a refrigerator. The sediment analysis should always be carried out immediately.

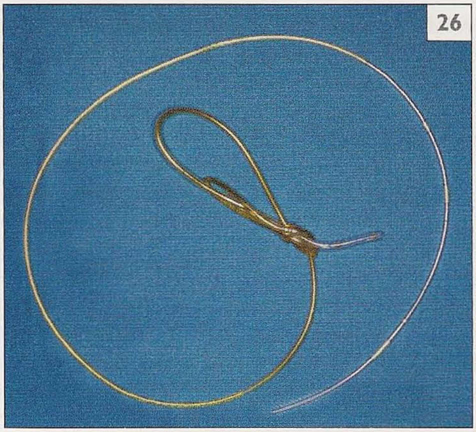
Urine specific gravity

Among other things, the specific gravity gives information on the concentration capability of the kidneys and should be determined with a refractometer. Determination with urine dipsticks is not sufficiently accurate (**27**).

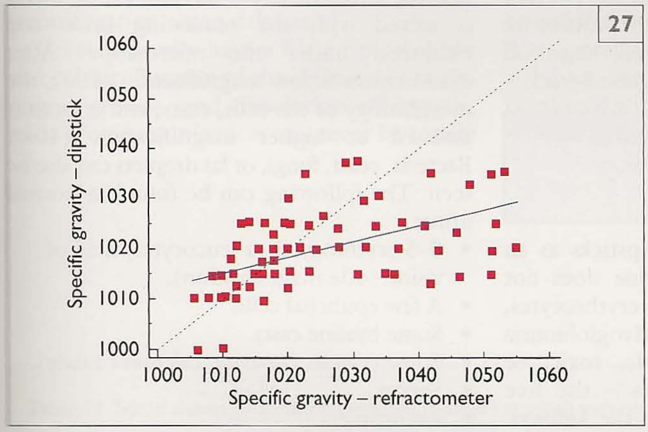
Urine dipsticks

Urine dipsticks for use in humans can be used for dogs and cats (**28**), with the exception of a few individual parameters. Indicators of leucocytes, nitrites, and urobilinogen give incorrect results and should not to be taken into account.[113,114] However, the determination of pH, protein, blood/haemoglobin, glucose, bilirubin, and ketone bodies is reliable. Specific veterinary dipsticks offer no advantages over the dipsticks used in human medicine, as they are not specially designed for animals; the same reservations and problems seen with human dipsticks apply.

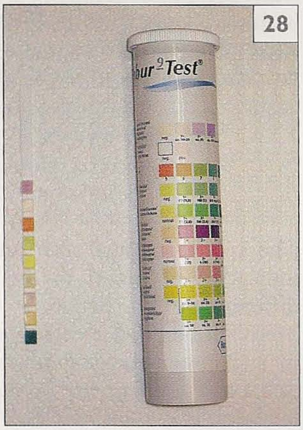
Carnivores normally produce acidic urine, as the kidneys regulate the acid–base status through the excretion of protons, ammonium ions, and phosphorous. Feeding times and diurnal fluctuations have a significant influence on the urinary pH, with less acidic urine being produced shortly after a meal (also described as the 'postprandial alkaline flood'). Drugs can also affect the results, e.g. furosemide and methionine lead to acidification, and sodium bicarbonate and chlorothiazide lead to alkalinization. Usually, the pH of dog and cat urine is between 6.0 and 7.5 (*Table 10*). Prolonged storage of urine prior to examination can also affect the pH of the urine. If an accurate pH is crucial for a diagnosis or treatment, a specific mobile or permanently installed pH-measuring device should be used, as the results obtained with urine dipsticks or pH paper are too variable.[115]



26 Knot in a urinary catheter after the length was not measured correctly.



27 The scatter diagram of urine specific gravity measured with a refractometer (X-axis) and with dipsticks (Y-axis) clearly shows that the correlation between the two measurement methods is poor.[112]



28 Example of a urinary dipstick used in human medicine that is suitable for use in veterinary medicine.

Table 10 Causes of acidic and alkaline urine.

Acidic urine	Alkaline urine
Respiratory and metabolic acidosis	Intake of low-protein food
Diabetic ketoacidosis	Urinary tract infection with urease-producing organisms (see *Table 8*)
Acute renal failure	Chronic vomiting
Acute severe vomiting or diarrhoea	Respiratory or metabolic alkalosis
High fever	Old urine specimen

Proteins are only normally present in the urine in very small quantities. There is a wide range of causes of proteinuria and the semiquantitative details provided by dipsticks should always be interpreted with respect to the specific gravity. Mild proteinuria (1+) in concentrated urine with a specific gravity of >1.050 may still be physiological, whereas the same amount of protein (1+) with a specific gravity of 1.005 is probably pathological. It is also important that the amount of protein is interpreted with respect to the other urine findings (dipsticks, sediment examination), clinical examination, and blood tests, to determine the origin of the protein loss or its aetiology. Preglomerular and glomerular proteinuria are of little significance for urolithiasis. Postglomerular proteinuria is indicative of inflammation of the lower urinary tract, a common finding in urolithiasis (with or without bacterial infection). Other causes are FLUTD, neoplasia, trauma, haemorrhage, and inflammatory conditions of the genital tract.

> Proteinuria can be classified as preglomerular, glomerular, or postglomerular.

The colour change seen on dipsticks as an indication of blood in the urine does not differentiate between erythrocytes, haemoglobin, and myoglobin. Myoglobinuria is a consequence of traumatic, toxic, or ischaemic damage to myocytes – the free myoglobin is then excreted via the kidneys. Haemoglobinaemia is usually a consequence of intravascular haemolysis – the free haemoglobin is excreted via the kidneys resulting in haemoglobinuria. Erythrocytes can find their way into the urine as a result of numerous disorders of not only the upper and lower urinary tracts, but also of the genital tract. Urolithiasis is an important differential diagnosis in micro- or macrohaematuria.

A colour change on the 'glucose' part of the dipstick is usually seen when the renal threshold for glucose is exceeded (in the dog: 10–12.2 mmol/l; in the cat: 14.4–17.2 mmol/l glucose in the blood), including in diabetes mellitus. In the cat, stress hyperglycaemia can also lead to glucosuria.[116] The role of glucosuria in urolithiasis is related to the fact that glucose is an ideal culture medium for bacteria; bacterial urinary tract infections are a common complication of glucosuria.

Ketone and bilirubin on the dipsticks provide additional information for the urinary examination, but are seldom of any relevance in cases of urolithiasis.

Sediment

Sediment analysis – especially if urinary stones are present – is an integral part of the urinary examination, and various crystals can provide an indication of the composition of the stones. It is therefore important to carry out the sediment analysis correctly and immediately. The urine sample (approximately 5 ml) is centrifuged in a tapered flask at a relatively low speed (1500–2000 rpm) for 5 minutes. The supernatant is almost completely decanted (leaving a residue of 0.5 ml) and the sediment is mixed with the remaining urine and examined under the microscope. After examination at low magnification (10×), the morphology of the cells, casts, and crystals is assessed at higher magnification (40×). Bacteria, yeast, fungi, or fat droplets can also be seen. The following can be found in normal urine:

- 0–5 erythrocytes or leucocytes/field of vision (40× magnification).
- A few epithelial cells.
- Some hyaline casts.
- Some crystals (struvite, calcium oxalate).
- Sperm.
- Fat droplets.

It is important to take the urine sampling method into consideration, since midstream urine almost always contains higher numbers of leucocytes (from the vagina, urethra, or prepuce) and possibly bacteria as well, whereas epithelial cells are more common in urine that has been withdrawn with a catheter. Finally, urine obtained by cystocentesis or catheterization contains higher numbers of erythrocytes than a midstream sample.

> Sediment analysis should always be performed immediately after urine collection, otherwise there is a risk that crystals may dissolve or form.

The term 'crystal' comes from the Greek *krystallos* meaning 'ice'. It is used to describe the solid phase of a substance with a specific internal structure, surrounded by symmetrically arranged flat surfaces. Crystals form when the urine is supersaturated with the relevant substances; the presence of crystals is therefore a risk factor for urolithiasis.

> Some forms of crystalluria are physiological and do not cause urolithiasis.

The evidence of crystals in the urine can be of diagnostic, prognostic, and therapeutic relevance, especially if urolithiasis has been diagnosed in the animal. Various factors influence crystal formation, such as *in vivo* urinary pH and the concentration and solubility of the substance, or the *in vitro* temperature, evaporation, and the technique used for analysis (centrifugation, urine stabilizers).

Crystals usually have a fairly typical shape and colour. Because of the differences in the origin, growth, and dissolution of crystals, microscopic examination can never be totally reliable. A definitive diagnosis can only be obtained using optical crystallography, infrared spectrometry, or x-ray diffraction. Nevertheless, microscopic identification of crystals in the sediment is helpful and easy to perform (*Table 11*, 29).

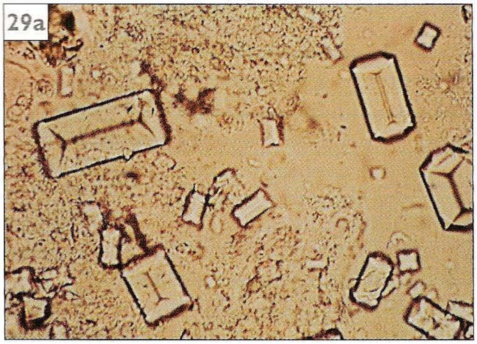
Urine bacteriology

Bacteriological examination of urine is the gold standard in diagnosing a bacterial urinary tract infection. However, it is important that the urine is collected prior to the administration of antibiotics. A bacteriological urinary examination also helps to detect potential antibiotic resistance, a problem that has manifested itself more and more frequently in veterinary medicine recently.[117]

As urine itself is a good culture medium, and the bacterial count can double every 20–45 minutes at room temperature, a culture should be initiated within 30–60 minutes of collection. Alternatively, commercially obtainable urine stabilizers can also be used; when stabilizers are combined with cooling, the bacterial content remains stable for up to 72 hours.[118]

Table 11 Typical shapes of urinary crystals and urine pH at which they normally occur.

Type of crystal	Shape	Acidic	Neutral	Alkaline
Struvite	Three- to six-sided, colourless prism, 'coffin-lid'	-	+	+
Calcium oxalate dihydrate (weddellite)	Small, colourless, envelope-shaped (octahedral)	+	+	-
Calcium oxalate monohydrate (whewellite)	Dumbbell, long oval and ellipsoid shape	+	+	±
Calcium phosphate	Pseudoamorphous	-	+	+
Ammonium urate	Yellowish brown, spherical	-	+	+
Cystine	Hexagonal	+	+	±
Xanthine	Reddish-brown, spherical	+	+	±
Sodium urate	Needle-shaped		+	+
Uric acid	Fine crystalline, whetstone-like	+	-	-
Brushite	Basalt columnar	±	+	±



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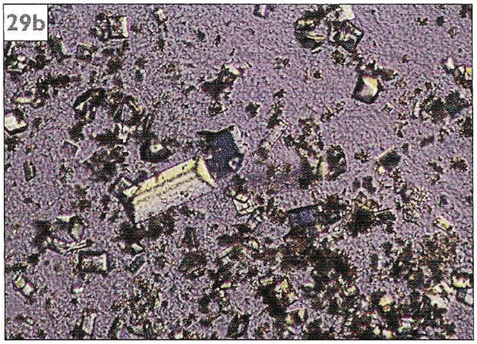

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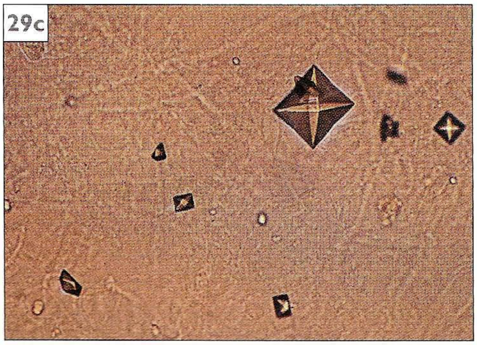

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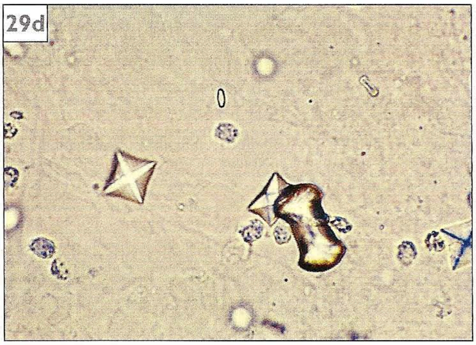

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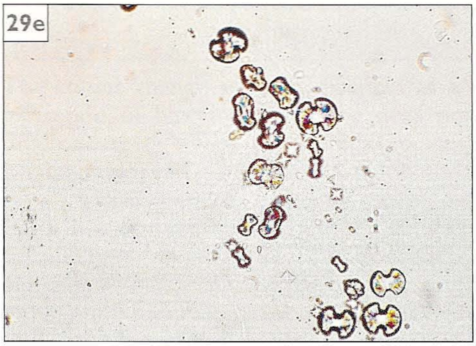

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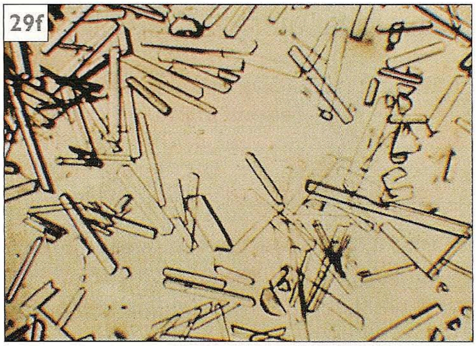

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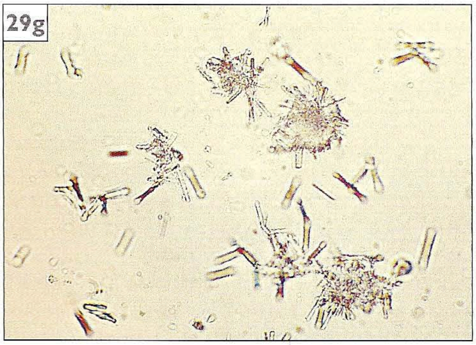

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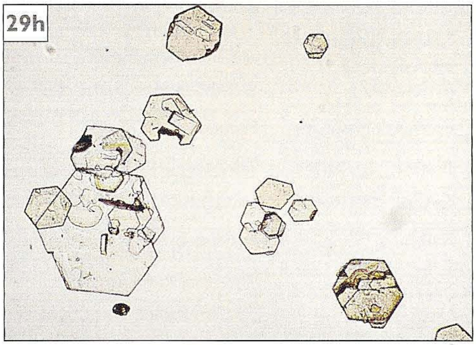

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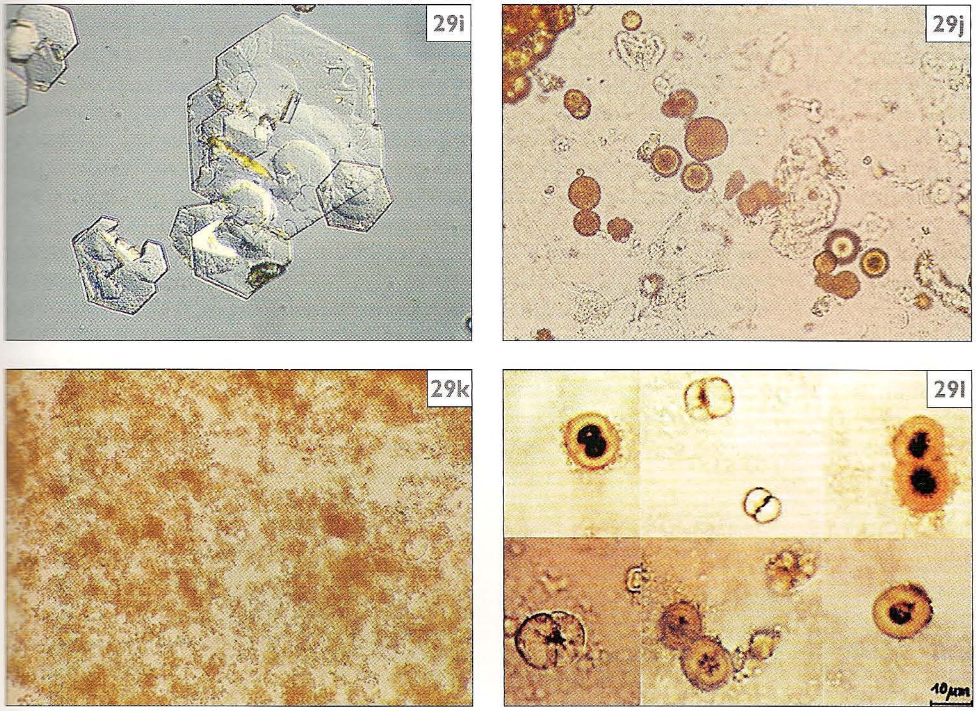


29 Crystals in the urine: (**a**) Struvite (magnesium ammonium phosphate hexahydrate), coffin-lid-shaped crystals, bright field. (**b**) Large struvite crystal and several weddellite (calcium oxalate dihydrate) crystals, as well as fine crystalline to pseudoamorphous, dark carbonate apatite (calcium phosphate containing carbonate), interference contrast. (**c**) Weddellite (calcium oxalate dihydrate) crystals, envelope-shaped, interference contrast. (**d**) Whewellite (calcium oxalate monohydrate) crystal, dumbbell shape, and weddellite crystals, bright field. (**e**) Whewellite (calcium oxalate monohydrate) crystal colony, dumbbell shape, bright field. (**f**) Brushite (calcium hydrogen phosphate dihydrate) crystals, basalt columnar structure, bright field. (**g**) Brushite (calcium hydrogen phosphate dihydrate) crystals, fine crystalline, basalt columnar and needle-shaped structure, bright field. (**h**) Cystine crystals, characteristic hexagonal plates, bright field. (**i**) Cystine crystals, interference contrast. (**j**) Ammonium hydrogen urate crystals, spherical shape with radial beam structure, bright field. (**k**) Uric acid, fine crystalline to pseudoamorphous (brick dust), bright field. (**l**) Xanthine crystals.[289]

Urine samples can be stored for up to 6 hours in the refrigerator without entailing significant bacterial growth.[119]

Although urine is normally sterile in the bladder, contamination with local bacteria from the distal urogenital tract can occur during catheterization. In healthy animals, both in the distal urethra of the male dog and in the vagina of the female dog, a multitude of bacteria can be present, including *Staphylococcus*, *Streptococcus*, *Mycoplasma*, *Klebsiella*, *Escherichia*, or *Corynebacterium*.[120] Although contamination can arise from resident skin flora even during cystocentesis, this technique of withdrawing urine is preferred for bacteriological culture. Spontaneous urine (midstream urine) is often contaminated by bacteria from the distal urogenital tract and is therefore unsuitable for bacteriological examination. If urinary stones are removed surgically, a bladder mucous membrane biopsy should be taken for bacteriological culture at the same time – this examination is more reliable than a urinary culture.[121,122]

In the dog, 75% of all bacterial urinary tract infections are caused by one bacterium, 18% by two bacteria, and 6% by three bacteria.[123] Similar results are found in the cat.[124] Quantitative urinary culture is used to determine whether a significant infection is present as opposed to simple contamination (*Table 12*).

Biochemistry

All animals with urolithiasis should have a blood test. This will provide evidence of any renal damage and the possible causes thereof.

The two most important parameters for assessing renal function are urea and creatinine. Both increase if the glomerular filtration rate falls. Creatinine is the more reliable parameter; it is partially dependent on the animal's muscle mass. Urea is the product of protein catabolism. It is formed in the urea cycle in the liver, and its serum concentration is more dependent on external factors, in addition to a reduced glomerular filtration rate, than that of creatinine. An increase in urea and creatinine is described as azotaemia. The latter is classified into prerenal, renal, or postrenal. Prerenal azotaemia is caused by insufficient renal blood supply, e.g. from dehydration. Postrenal azotaemia occurs when urine excretion from both kidneys is markedly diminished or is absent, e.g. in the event of bladder stones or an obstruction caused by FLUTD. Postrenal azotaemia does not usually occur if only one kidney is affected (e.g. by a kidney stone), unless the contralateral kidney is also damaged. Phosphorus is excreted via the kidneys, and usually increases in the event of azotaemia.

Besides urea, creatinine, and phosphorus, other biochemical parameters are also important. An acute urinary obstruction frequently leads to hyperkalaemia, as potassium can no longer be excreted. A sharp increase in serum potassium can cause bradycardia (atrial standstill). Such cases require emergency intensive care.

In the healthy animal, serum calcium is kept within very narrow limits, but can decrease or increase in the event of delayed chronic renal failure. However, it is important to determine whether the hypercalcaemia may be the cause of the renal failure. Ideally, ionized calcium is measured, because this gives a more accurate reflection of the actual serum calcium level. Occasionally, hypercalcaemia may result in calcium oxalate stone formation.[125,126] Possible causes of hypercalcaemia include primary hyperparathyroidism, and tumours such as lymphoma, anal glandular adenocarcinoma (malignancy-induced hypercalcaemia), or bone tumours (osteosarcoma, multiple myeloma). In cats, up to 40% of cases of hypercalcaemia are idiopathic.

Dogs with urate stones can have a primary hepatopathy, e.g. portosystemic shunt. Classically, reduced urea and serum protein levels are found. In the event of a congenital shunt, the hepatic enzymes are usually within the reference range since this disorder does not induce any hepatocellular damage. A tentative diagnosis can be confirmed with hepatic function tests, such as measuring pre- and postprandial serum bile acid. Acquired hepatopathies are a less common cause of urate stones and can often be diagnosed on the serum biochemistry profile.

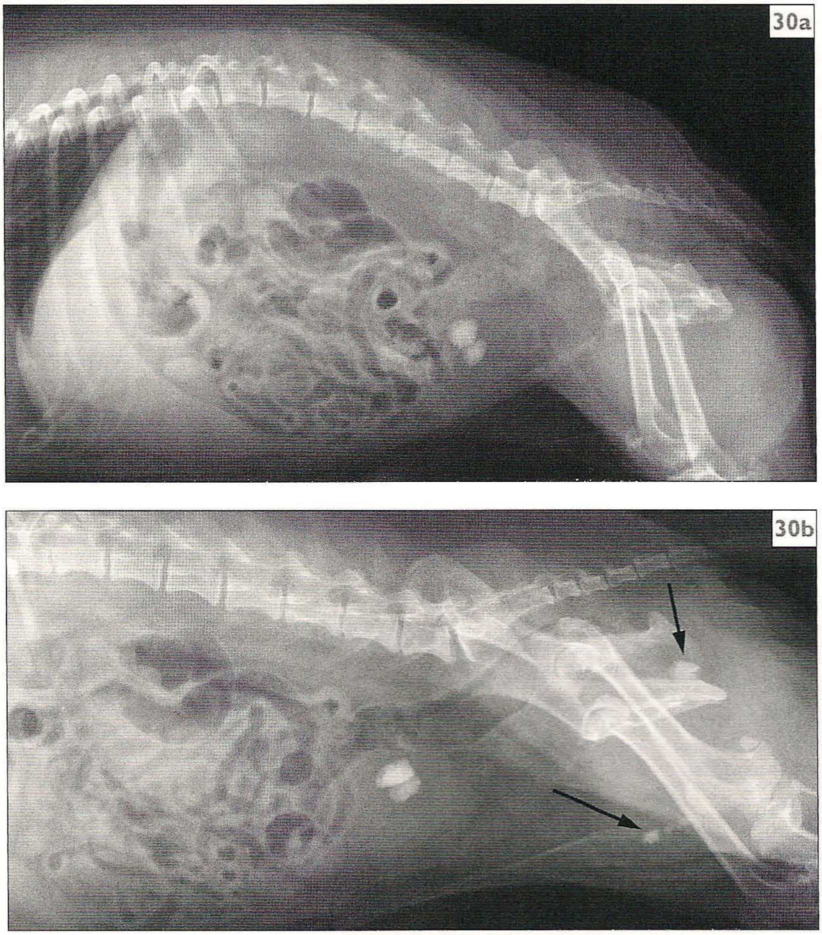
Table 12 Interpretation of the quantitative bacterial content. The figures represent colony-forming units (CFUs) per ml of urine.

Collection method	**Significant**		**Suspicious**		**Contamination**	
	Dog	Cat	Dog	Cat	Dog	Cat
Cystocentesis	≥1,000	≥1,000	100–1,000	100–1,000	≤100	≤100
Catheterization	≥10,000	≥1,000	1,000–10,000	100–1,000	≤1,000	≤100
Midstream	≥10,0000	≥10,000	10,000–90,000	1,000–10,000	≤10,000	≤1,000

Diagnostic imaging

Diagnostic imaging, such as plain radiography, contrast radiography, or ultrasound examination are essential in assessing urolithiasis. Such procedures often make it possible to determine the location, number, and consequences of urinary stones, as well as their characteristic features (size, shape, radiological density, and number).

As many urinary stones in animals are radiopaque, they can often be seen on *plain radiographs*. The colon should be emptied prior to radiography, using an enema if necessary, otherwise urinary stones in the ureters or in the urethra can be overlooked. In male animals, the hindlimbs should be positioned in such a way that the urethra is not overshadowed, e.g. by fully extending both hindlimbs in caudodorsal extension (**30**). Less radiopaque urinary stones such as urate stones are often easier to visualize with *contrast radiography*. Intravenous urography (IVU) has proven useful for the



30 Radiographs of an 8-year-old neutered male West Highland White Terrier with (**a**) normal positioning of the hindlegs and (**b**) in full caudal extension. On the first film, two irregular stones can be seen in the bladder, but the stones above the os penis and in the pelvic flexure (arrow) of the urethra can only be seen clearly on the second film. These stones were all 100% calcium oxalate.

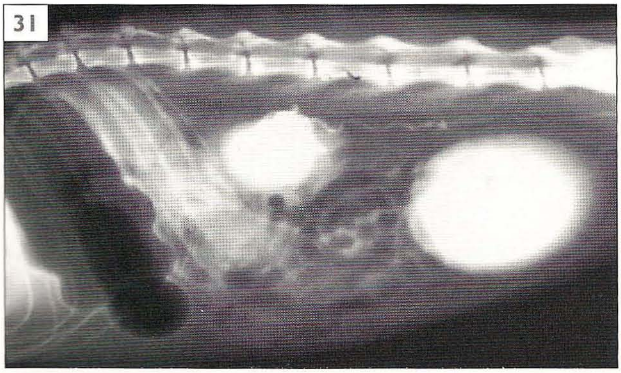
detection of stones in the upper urinary tract (kidneys and ureters), or retrograde cystography for detecting stones in the lower urinary tract (bladder and urethra) (**31**). Intravenous urography is usually carried out under general anaesthesia; 700 mg/kg of an iodine-based contrast medium are administered rapidly via an intravenous catheter and ventrodorsal views taken after 5 and 10 minutes, as well as a lateral view after 15 minutes. For *retrograde cystography*, an iodine-based contrast medium (2 ml/kg, 1:1 iodine-based contrast medium diluted with NaCl), air (2 ml/kg), or both (to produce a double contrast image) can be used. The urinary catheter is prefilled with contrast medium and inserted only a few centimetres into the urethra, the distal urethra is held firmly round the catheter using atraumatic forceps and the radiograph is taken as the contrast medium is being injected.

> If urolithiasis is suspected, it is important to display the entire urinary tract on the film, i.e. the entire urethra should be visible. For retrograde cystography, the urinary catheter should not be inserted into the bladder; it should lie just inside the urethra of the male dog/cat or in the vestibule of the female dog/cat.

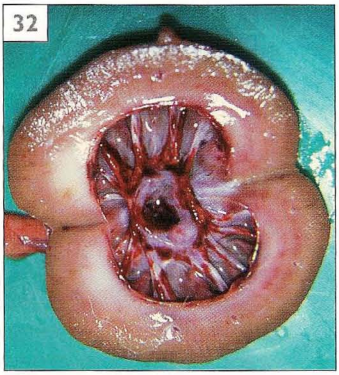
Ultrasound imaging enables both radiopaque and radiolucent urinary stones to be visualized in the kidneys, ureters, bladder, and cranial urethra. A urinary obstruction caused by ureteral stones usually leads to dilatation of the ureter and renal pelvis and, depending on the duration of the obstruction, to mild to severe hydronephrosis (**32**). Urinary stones can be identified as hyperechoic structures with distal acoustic shadows (**33**) and can normally be easily distinguished from air or masses in the bladder. Ultrasound imaging also enables the visualization of stones in the remaining urinary tract (**34**).

The sensitivity (i.e. numbers of false negatives) depends on the composition of the urinary stones (*Table 13*) and on their size and location. In addition to the initial diagnosis of urinary stones, imaging procedures can be used to determine their numbers, which is especially useful following dissolution or at check-ups. Here, too, the composition of the stone has a direct impact on correct estimation of their numbers (*Table 14*).

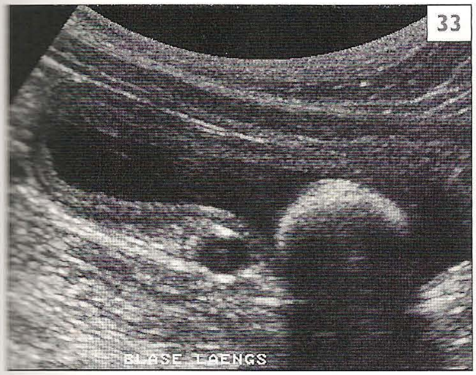
Modern imaging procedures such as *computed tomography* (CT) or *magnetic resonance imaging* (MRI) are rarely used in veterinary medicine for diagnosing urolithiasis and are not usually necessary.



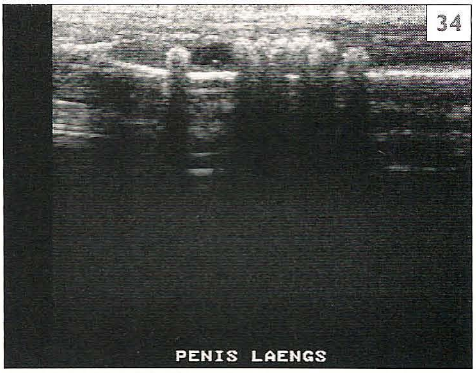
31 Intravenous urography of a cat with a stone obstructing the ureter, which induced hydronephrosis.



32 Hydronephrosis in a Welsh Corgi with a ureteral stone.



33 Ultrasound image of a 100% ammonium urate bladder stone in a 5-year-old neutered male Dalmatian.



34 Seven small urethral stones directly above the os penis can be clearly seen in this 7-year-old male West Highland White Terrier with distal acoustic shadows.

Table 13 The diagnostic sensitivity (percentage false negatives) of various imaging techniques for different urinary stones in the bladder.

	All types of stone	Struvite	Calcium oxalate monohydrate	Ammonium urate	Cystine	Brushite	Silica
Plain radiograph	13%	2%	5%	25%	25%	20%	5%
Pneumocystogram	7%	0%	7%	20%	2%	10%	10%
Double contrast radiograph	5%	0%	10%	10%	0%	5%	0%
Ultrasound imaging (5 MHz)	4%	0%	2%	12%	2%	7%	2%
Ultrasound imaging (7.5 MHz)	3%	0%	2%	10%	6%	3%	2%

Table 14 Probability of finding the correct number of different urinary stones in the bladder using various imaging techniques.

	All types of stone	Struvite	Calcium oxalate monohydrate	Ammonium urate	Cystine	Brushite	Silica
Plain radiograph	38%	20%	40%	30%	20%	40%	65%
Pneumocystogram	45%	30%	40%	35%	40%	60%	65%
Double contrast Radiograph	55%	50%	20%	50%	65%	60%	70%
Ultrasound imaging (5 MHz)	43%	15%	48%	28%	44%	37%	53%
Ultrasound imaging (7.5 MHz)	54%	50%	58%	35%	50%	50%	63%

Cystoscopy is useful for assessing the size, number, and appearance of stones (**35**), as well as for measuring lesions in the urethra and the bladder (**36**), diagnosing radiolucent stones in the urethra in suspected cases (e.g. filling defect in contrast medium on radiograph) and for the endoscopic removal of small stones. In female dogs, rigid endoscopy with a 3 mm scope has proved useful, but a flexible endoscope can also be used. A flexible endoscope with an external diameter of up to 3.7 mm can usually be inserted with ease in male dogs >5 kg, whereas a diameter of up to 2.7 mm is more suitable for smaller male dogs. In female cats and tomcats >1.5 kg, it is only possible to pass through the urethra with a 1 mm diameter endoscope; flexible and semirigid endoscopes are available for this purpose.

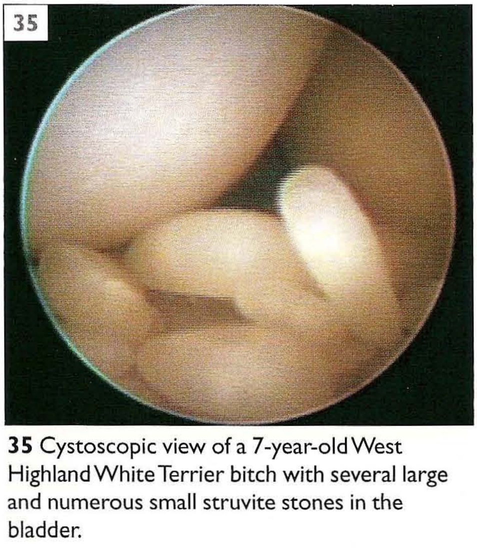
URINARY TRACT OBSTRUCTION

Urethral obstruction is a fairly common problem in animals with urinary stones or cats with FLUTD. Obstructions are more common in male than in female animals.

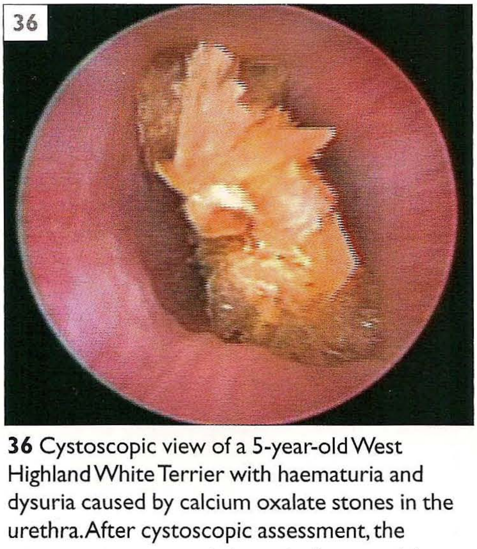
A urinary tract obstruction should be treated as an emergency; untreated cases result in a rapid deterioration in the general status and may even prove life-threatening due to shifts in the electrolyte and acid–base balances.

A urethral obstruction can cause shock with reduced perfusion, which in turn leads to azotaemia, metabolic acidosis, hyperkalaemia, hyperphosphataemia, and hypocalcaemia. Reduced hydrogen ion excretion results in metabolic acidosis. Lactic acidosis, caused by the reduced cardiac output, can further upset the acid–base imbalance. A marked reduction in blood pH (often <7.2) affects the respiratory, cardiovascular, and central nervous systems. It increases ventilation by increasing respiration rate and/or tidal volume. Cardiac arrhythmias and a reduced cardiac output are often found. Finally, it can cause a range of CNS (central nervous system) signs from lethargy to coma. Reduced perfusion and azotaemia exacerbate the CNS signs.

Hyperkalaemia is a result of reduced potassium excretion, but the release of potassium from cells also causes acidosis. As potassium is critical for maintaining the resting potential of cells, an increase initially leads to increased cellular excitability; in severe cases of hyperkalaemia, the resting potential is less negative than the action potential and the cells cannot repolarize after depolarization. Clinically, these effects are primarily seen in muscle tissue and the cardiac conduction system (bradycardia).



35 Cystoscopic view of a 7-year-old West Highland White Terrier bitch with several large and numerous small struvite stones in the bladder.



36 Cystoscopic view of a 5-year-old West Highland White Terrier with haematuria and dysuria caused by calcium oxalate stones in the urethra. After cystoscopic assessment, the stones were removed via urohydropropulsion.

Emergency treatment

Although the ultimate aim of treatment is to remove the obstruction, the patient must first be stabilized. The highest priority is intravenous fluid administration to correct acid–base imbalances, electrolyte disturbances, and azotaemia. Both 0.9% NaCl, which does not contain any potassium, and lactated Ringer's solution, which achieves a better acid–base balance, have proven to be equally successful. As animals show a marked increase in diuresis after the removal of an obstruction, the amount of fluid administered must be suitably adapted – this can be >8 ml/kg/hr. Ideally the amount of fluid given should be related to central venous pressure measurements. In some cases the infusion rate should be monitored hourly and adapted accordingly. Should the central venous pressure drop in spite of appropriate fluid therapy, a colloidal solution can be given intravenously (e.g. hydroxyethyl starches).

> Intravenous fluid administration must be the first step in treating an obstructed patient prior to the instigation of further diagnostic and therapeutic measures.

Animals diagnosed with haemodynamic problems due to hyperkalaemia, should also be treated for electrolyte and acid–base imbalance. The cardiovascular effects of hyperkalaemia can be treated with calcium gluconate 10% (50–100 mg/kg), this often resolves hypocalcaemia at the same time. Calcium has no direct influence on the serum potassium concentration, but leads to a normalization of the differences between the resting potential and the action potential. The intravenous administration of regular insulin (0.1–0.25 IU/kg) causes glucose and potassium to shift into cells – the serum potassium concentration drops and the resting potential normalizes. Regular insulin should usually be administered with glucose. Non-diabetic animals can also be given intravenous glucose alone; the release of endogenous pancreatic insulin will have the same effect. The final possibility for treating hyperkalaemia is the administration of sodium bicarbonate; one third of the dose calculated using the formula: 0.3 × base deficit × kg body weight, should be administered over a period of 15–30 minutes. Sodium bicarbonate enables the shift of potassium into the cells and resolves metabolic acidosis. Sodium bicarbonate should only be given if the blood pH is <7.1 and a blood gas analysis must be carried out afterwards.

Once the patient is haemodynamically stable, the obstruction should be removed as quickly as possible. Sometimes a plug can be seen at the tip of the penis, which can be removed using massage (see **25**). Plugs can be partly removed by catheterization and hydropropulsion. See below for details on urohydropropulsion and surgery. The bladder should only be emptied using cystocentesis if the blockage cannot be removed using a catheter. The bladder wall in obstructed animals is often badly damaged and there is a serious risk of rupture and subsequent uroabdomen if the technique is carried out without due care.

Anaesthesia and analgesia

Urinary tract obstructions are very painful and most animals should be sedated or anaesthetized prior to removal of the obstruction. Electrolyte and acid–base imbalances must be corrected before anaesthesia. The administration of neuroleptanalgesia has been well proven. A suitable combination is an opioid (e.g. buprenorphine 6–10 μg/kg IV, IM, or SC) with a benzodiazepine (e.g. diazepam 0.2–0.5 mg/kg IV or midazolam 0.2–0.5 mg/kg IV, IM, or SC). The benzodiazepine helps to relax the outer urethral sphincter. If the level of sedation is not sufficient for catheterization, a low dose of ketamine (2 mg/kg IV) can be administered in cats. The dosage of ketamine should not be repeated and it should be avoided altogether in cats that have already been treated for an obstruction, as urethral stricture could complicate catheterization.

> Ketamine remains unchanged prior to renal excretion in cats and can accumulate in the body if the obstruction is not removed quickly.

Once the obstruction has been removed, analgesia should be continued. A single administration of a nonsteroidal anti-inflammatory drug (NSAID) (e.g. meloxicam) treats the inflammation and improves general wellbeing. Additional analgesia can be achieved using, for example, a fentanyl patch.[128]

STONE REMOVAL

Whether a stone requires removal depends on whether it is an incidental finding – on abdominal radiography, for example – or whether it is associated with clinical signs.

> Kidney stones are often asymptomatic or associated with minimal clinical signs (e.g. intermittent haematuria) and surgical excision is not immediately necessary.

The removal of symptomatic urinary stones depends upon various factors, such as location (*Table 15*), severity of signs, and stone composition; obviously other aspects such as recurrence, the animal's overall condition, and technical and financial considerations should not be overlooked.

Removal by diet/medication

Some stones can be dissolved with special diets or medication. The composition of the stones can be determined using various parameters (*Table 16*). It is important to monitor the success of such measures regularly using imaging (radiography for radiopaque stones, ultrasonography) and urinalysis. If stones initially shrink, but then stabilize or even resume growth, complicating factors should be considered. Possible causes include stones with a different core to exterior

Table 15 Possibilities for stone removal according to location.

Kidneys	Ureters	Bladder	Urethra
Diet/medication		Diet/medication	
Nephrotomy/nephrectomy	Ureterotomy	Cystotomy	Urethrotomy
		Urohydropropulsion	Antegrade or retrograde urohydropropulsion
Lithotripsy	Lithotripsy	Cystoscopy	Cystoscopy

Table 16 Likely stone composition based on various parameters.

Parameter	Struvite	Calcium oxalate	Urate	Cystine
Predisposed breeds	Miniature Schnauzer, Bernese Mountain Dog, Bull Terrier, Bichon Frisé	Miniature Schnauzer, Yorkshire Terrier, Bichon Frisé, Miniature Poodle	Dalmatian, English Bulldog, Yorkshire Terrier	Newfoundland, English Bulldog
Age (average)	7 years	8 years	3 years without shunt, 1 year with shunt	5 years
Sex	>80% female	>70% male	>85% male	>90% male
Urine pH	Alkaline	Slightly acid to slightly alkaline	Acid to neutral	Acid
Crystals	Coffin-lid-shaped	Envelope-shaped	Thorn-apple-shaped	Hexagonal
Radiopacity	++ to +++	+++	0 to +	+ to ++
Urinary tract infection	In dogs with urease-positive bacteria	Secondary only	Secondary only	Secondary only
Concomitant disease	Poor immunity to urinary tract infection	Hypercalcaemia, hyperadrenocorticism	Hepatic shunt	None

composition, unsuccessful treatment for urinary tract infection, or lack of compliance from the owner for the administration of drugs or diet. A detailed description of the treatment and prevention of urolithiasis is given for each type of stone in Chapters 2 and 3.

> The dissolution of ureteral or urethral stones is contraindicated, since such cases are almost always emergencies.

Surgical removal

Surgical removal is the method of choice for all *symptomatic* ureteral stones, for kidney stones that cannot be dissolved by diet or medication, and for bladder and urethral stones that cannot be dissolved or removed by urohydropropulsion. Surgery should also be considered in cases where owner compliance makes medication or nutritional management impossible. Obstructions combined with a urinary tract infection should be treated as surgical emergencies to avoid the danger of sepsis or peracute renal failure.

If surgical removal of kidney stones is indicated, a nephrotomy or pyelolithotomy is usually performed (**37**). Nephrectomies are only indicated for kidneys that have lost all function (confirmed by scintigraphy or intravenous urography). During surgery, the entire urinary tract should be carefully examined for any other stones. Stones may occasionally move backwards up the ureter, possibly as far as the renal pelvis, complicating the procedure.[129] The relevant texts on operating techniques should be consulted.[130] The most important complications of surgical stone removal from kidneys and ureters are renal failure (especially for bilateral surgery), haemorrhage, and urine leakage into retroperitoneal tissue.

Surgical removal of bladder stones is indicated when there is the presence of an anatomical predisposition to stone formation (urachal diverticulum), when symptomatic stones cannot be dissolved, or when biopsy of the bladder wall is required. Calcium oxalate stones cannot be dissolved and must be surgically removed as well. Obstructing stones in the urethra that cannot be washed out in either direction should always be removed surgically. Cystotomy (**38**) is preferable to urethrotomy, if the stones can be washed into the bladder preoperatively or intraoperatively. The relevant texts should be consulted for a detailed

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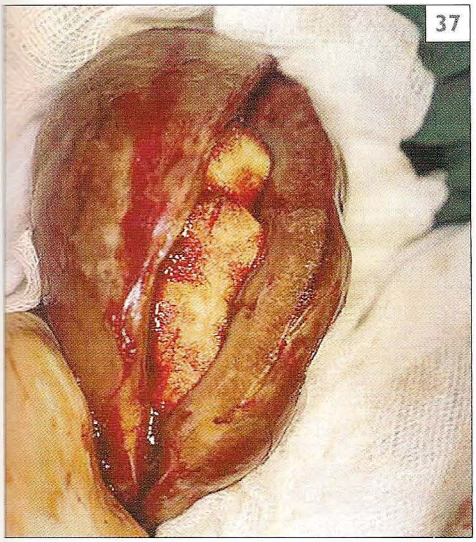

37 Nephrotomy in a 6-year-old Boxer with a calcium oxalate stone.

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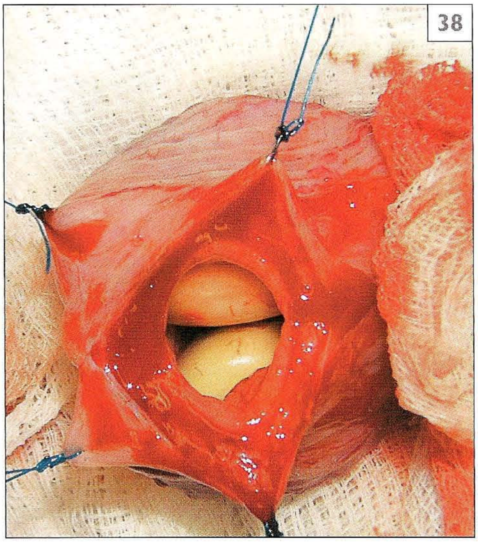

38 Cystotomy to remove multiple struvite stones from a 7-year-old West Highland White Terrier (see also **35**).

description of the surgical technique.[130] It is imperative to perform retrograde flushing of the urethra following removal of all bladder stones to check for any remaining stones that may have been washed down. A postoperative lateral radiograph (for radiopaque stones) should confirm that no stones have been overlooked. Complications of cystotomy are rare: there may be leakage of urine into the abdomen or bleeding into the bladder. Haemorrhage is relatively common following urethrotomy; strictures are rare.

Urohydropropulsion

Urohydropropulsion is used to flush one or more stones that are causing obstruction or dysuria out of the lumen of the urethra. If the bladder is very full, cystocentesis may be required prior to urohydropropulsion, to reduce pressure on the bladder wall. Sedation or anaesthesia is required, depending upon the animal's condition. The urethra is initially lubricated with a large volume of 1:1 physiological saline mixed with sterile water-soluble lubricant; this is instilled through a urinary catheter.

Male dog

An assistant compresses the lumen of the urethra via rectal palpation through the pelvic floor (ischial bone). A urinary catheter connected to a 50 ml syringe filled with sterile isotonic solution is then introduced into the lumen of the urethra through the glans; the glans is manually compressed around the catheter to set up a closed system between glans and pelvic floor. Saline is then injected under pressure into the urethra until the assistant feels the urethra expand (**39**).

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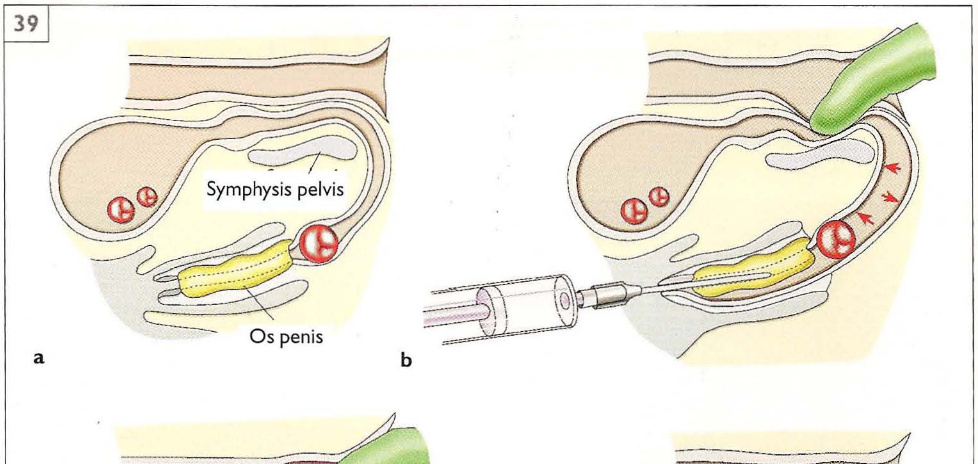

39 Urohydropropulsion in a male dog.

Enlargement of the urethra diameter must be distinctly felt, since this is the only way to achieve the widest possible lumen. The probability of rupturing the mucosa is minimal, since the isotonic solution in the lumen is much more likely to flow into the bladder. For small stones, compression at the glans can now be released and the catheter removed *immediately* to induce the antegrade washout of stones. Pressure on the pelvic floor is maintained or even increased anterior to this. It is usually necessary to repeat the procedure several times to displace small stones from the caudal end of the os penis (the point where stones most frequently lodge) to the glans. If the stones are too big to pass through the ventral notch in the os penis, they must be flushed back into the bladder. In this case, pressure on the pelvic floor is abruptly released while more liquid is injected by catheter into the lumen of the urethra. If the procedure has to be repeated several times before the stone enters the bladder, it may be necessary to reduce bladder pressure again by cystocentesis.

Bitch

A soft catheter is introduced as far as possible into the urethra. Using an index finger inserted into the rectum (or preferably the vagina), the distal end of the urethra is closed around the catheter to create a closed system between stone and compressed urethra (**40**). Saline is now injected under pressure into the urethra. The stone can usually be flushed back into the bladder by dilation of the urethra combined with fluid pressure. On rare occasions, it may be necessary to 'loosen' the stone by rectal palpation.

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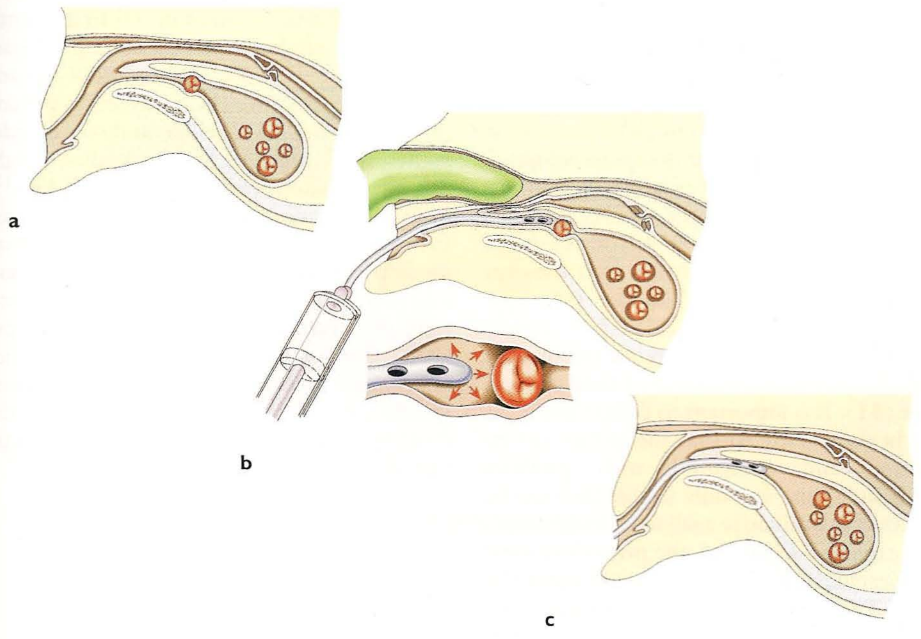


40 Urohydropropulsion in a bitch.

Antegrade voiding urohydropropulsion

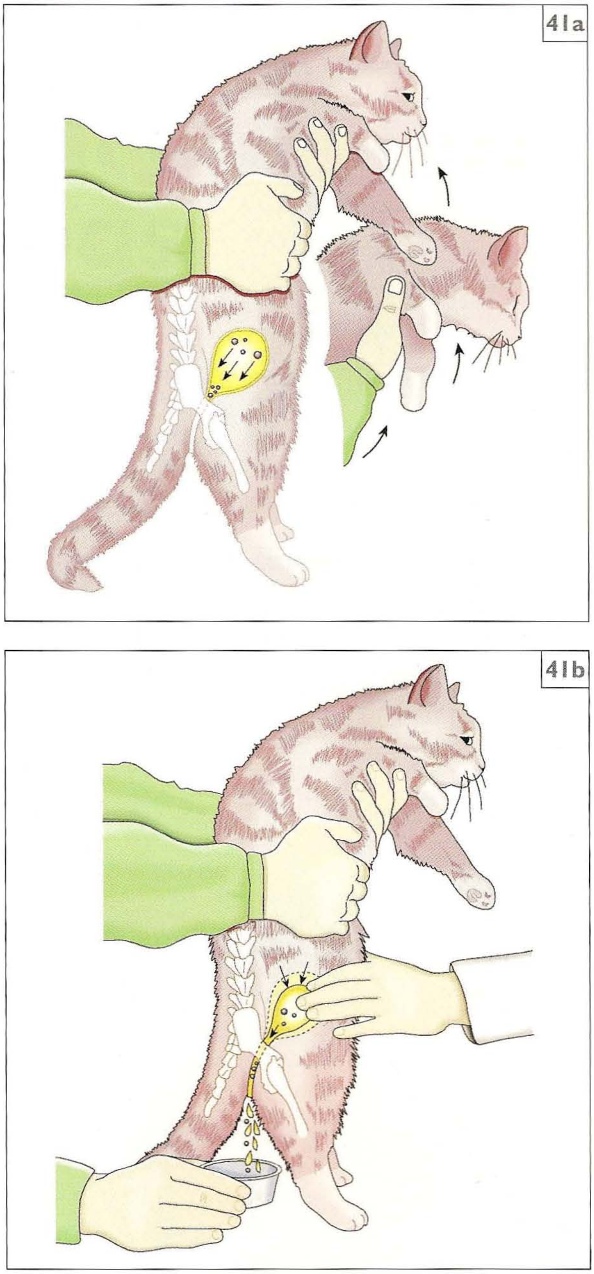
Small bladder stones can be flushed out via the urethra by antegrade voiding urohydropropulsion without the need for surgical intervention (**41**). It is vital to assess the size and shape of stones in relation to the patient before considering this method. The stone should be no bigger than the largest diameter of the expanded urethra at its narrowest point. For female cats, this is up to a maximum of 5 mm (body weight >4.5 kg); for male cats, up to a maximum of 1 mm; for bitches, up to a maximum of 6 mm (bodyweight >7 kg but <10 kg); for male dogs, up to a maximum of 5 mm (body weight >7 kg but <10 kg). As a rule, antegrade voiding urohydropropulsion works better on anaesthetized animals, although the procedure can also be performed in conscious patients (e.g. if anaesthesia is contraindicated). Medication to achieve analgesia and muscle relaxation should be given in both cases. An opioid in combination with benzodiazepine or propofol will produce the desired effect.

The bladder must be reasonably full prior to antegrade voiding urohydropropulsion; if necessary, sterile isotonic solution can be introduced into the bladder by catheter (up to 4–6 ml/kg body weight) until a medium-full bladder can be felt by manual palpation. The catheter must be removed before antegrade voiding urohydropropulsion. The patient can then be positioned so that the spinal column is roughly vertical. Anaesthetized patients must be well supported to prevent spinal or muscular injury. The bladder is shaken sufficiently for gravity to draw all the stones into the area around the neck of the bladder (trigone). Passage of urine is now aided by constant craniocaudal manual pressure on the bladder until all stones in the urethra are passed with the urine (**41**). It is important to collect this urine in a beaker, firstly so that the stones can be counted and compared with previous radiographs, and secondly so that they can be subjected to qualitative analysis. If fewer stones than expected are found, the procedure must be repeated. If the number of stones cannot be counted on the radiographs, the procedure is repeated until no more stones come out. Ultrasound examination or double contrast cystography is recommended to make sure that no more stones are present in the bladder or urethra.

Haematuria frequently occurs following antegrade voiding urohydropropulsion for a few hours (dogs) or days (cats). A further complication is obstruction of the urethra if a large stone remains stuck. (This can generally be washed back into the bladder by retrograde urohydropropulsion.) In animals with pre-existing urinary tract infection, antegrade voiding urohydropropulsion is indicated only following a cost–benefit analysis, since it can easily lead to pyelonephritis. Such animals must always be treated with an appropriate antibiotic prior to the procedure.

Lithotripsy

In human medicine, lithotripsy (or stone fragmentation) is an established treatment for symptomatic kidney and ureter stones, but there are few reports of it in veterinary medicine. A variety of equipment and techniques has been used, especially to reduce stones in the kidneys so that the fragments can be washed into the bladder with the urine. The success rate for first treatment in dogs is approximately 50%; kidney stones in cats are somewhat harder to break up.[131] In a recently published study into endoscopic laser lithotripsy, it was possible to break up and subsequently remove (by urohydropropulsion or endoscopy) all urethra and/or bladder stones in 18 dogs (13 female, median weight 8.5 kg; 5 males, median weight 8.3 kg).[132] Mild complications arose in three dogs because of low body weight. The most famous German medical dictionary, 'Pschrembel', contains, as a joke, a description of preliminary experimental trials of intracorporeal petrophage lithotripsy (IPL) using starved kidney-stone lice (*Petrophaga lorioti nephrotica*).[133] The name *Petrophaga lorioti* is derived from one of the most renowned German stand-up comedian, Loriot.



41 Antegrade voiding urohydropropulsion.

Hospital Veterinário de Trás-os-Montes

CHAPTER 2

Urinary stones in dogs

Struvite stones (magnesium ammonium phosphate hexahydrate)

Calcium oxalate stones

Calcium phosphate: carbonate apatite stones

Calcium phosphate: brushite stones

Ammonium urate stones

Sodium urate, potassium urate, and uric acid stones

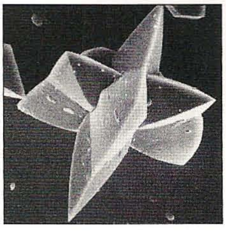
Cystine stones

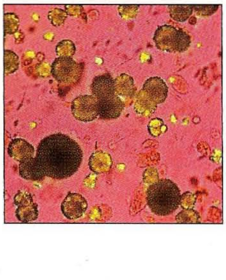
Xanthine stones

2,8-dihydroxyadenine stones

Silicate stones

Drug-induced urinary stones





Struvite stones (magnesium ammonium phosphate hexahydrate)

INTRODUCTION

Struvite stones (magnesium ammonium phosphate hexahydrate – $MgNH_4PO_4 \cdot 6H_2O$) are mostly white to light yellow; the surface can be microcrystalline and worn smooth. Many stones also have very well formed crystal structures at the surface (**42, 43**). They present as multiple stones or large single stones predominantly in the bladder.

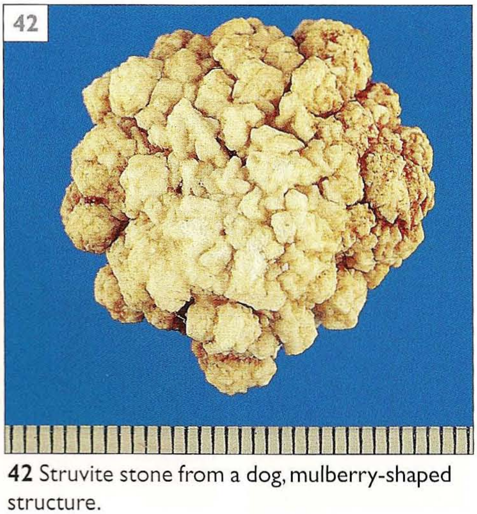
EPIDEMIOLOGY

In the past, struvite stones were the most common form of stone in dogs. During the 1990s, this trend changed, particularly in the USA, in favour of calcium oxalate stones (*Table 17*). Although the percentage of struvite stones has declined in other regions as well, this does not mean that the absolute incidence rate has decreased. Struvite stones appear to be more common in certain breeds (*Table 18*).

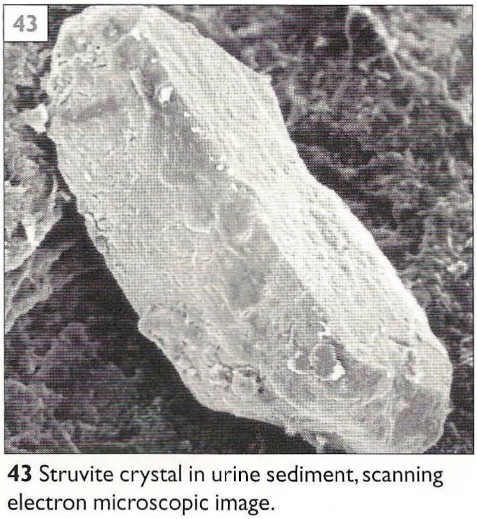
Since struvite stones in dogs are primarily linked to urinary tract infections, it is possible to assume a susceptibility to urinary tract infections in predisposed breeds such as the Pekingese, Cocker Spaniel, and Shih Tzu. The short urethra of female animals predisposes them to urinary tract infections; an increased incidence of struvite stones is therefore to be expected in the bitch. This is confirmed in the overall evaluation of the animals in *Table 18* where the female:male ratio = 1:0.75 (n = 7,697); it is also seen in a European study, with both entire and neutered dogs (female:male ratio = 1:0.49)(**44**).[8]

Struvite stones in dogs are primarily linked to urinary tract infections.

In Germany, struvite stones are predominantly found in female animals of certain breeds, e.g. the Pekingese (female:male ratio = 1:0.4) and Shi Tzu (female:male ratio = 1:0.4).[10] A Canadian study also found that struvite stones have a higher prevalence in female dogs in the following breeds: Miniature Schnauzer, Shih Tzu, Bichon Frisé, Lhasa Apso, and Yorkshire Terrier.[24] However, there are some breeds where the males have more struvite stones than the females,e.g. Bernese Mountain Dog (female:male ratio = 1:4.8), Cocker Spaniel (female:male ratio = 1:1.9) and German Shepherd Dog (female:male ratio = 1: 3.0).[10] Beside urinary tract infections, the obstruction of urinary flow due to gravel through the long urethra is a contributory factor in male dogs. The predominant occurrence of struvite stones in specific breeds is accounted for in some publications by the formation of stones under sterile conditions.[9,134]



42 Struvite stone from a dog, mulberry-shaped structure.



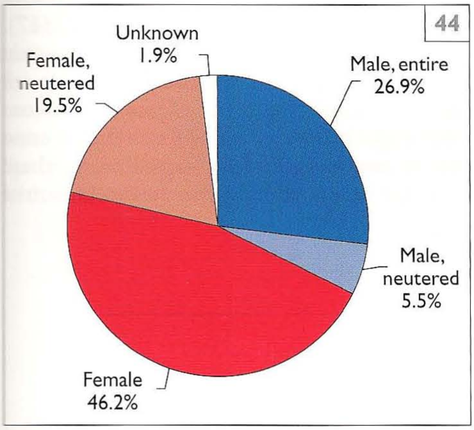
43 Struvite crystal in urine sediment, scanning electron microscopic image.

Struvite stones are significantly more common in female dogs than in male dogs.

The average age of dogs with struvite stones according to one European study was 7.0 years[8] (45) (USA: 5.9 years[7]) but struvite stones can also occur in dogs less than 1 year old.

Table 17 Changes in the percentage of dogs presenting with struvite stones (1984–2003).

Country	Date	Percentage of struvite stones
USA	1984	70%[318]
	1997	45%[28]
Germany	1990–1992	61%[8]
	1999–2001	54%[8]
Canada	1998–2003	44%[29]
Czech Republic	1997–2002	39%[23]
Benelux	1994	5%[24a]
	2003	40%[24a]

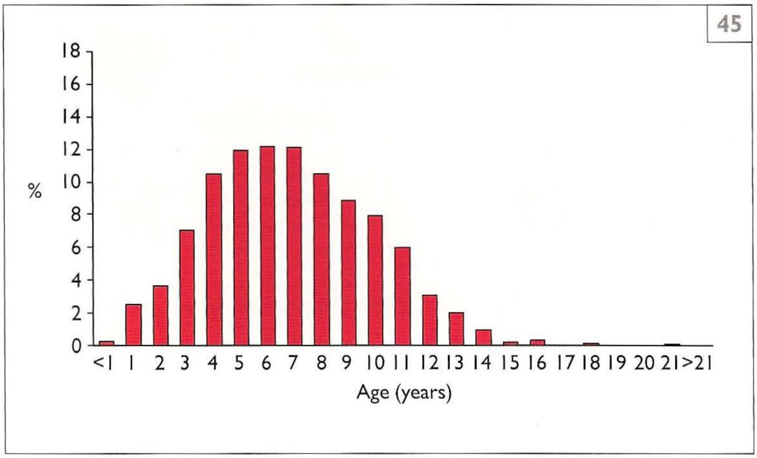


44 Gender distribution of dogs with struvite stones, European study 1999–2001 (total number n = 4,082; struvite stones n = 1,991).[8]

Table 18 Breeds of dog in whom struvite stones predominate (total number of stones, n = 4,996).[8]

Breed (total number of stones)	Share of struvite stones (%)
Bernese Mountain Dog (n = 90)	96
Bull Terrier (n = 68)	91
Golden Retriever (n = 53)	91
Pekingese (n = 186)	85
Cocker Spaniel (n = 379)	85
German Shepherd (n = 111)	84
Shih Tzu (n = 194)	81
Crossbreed (n = 1,365)	68
West Highland White Terrier (n = 169)	62
Lhasa Apso (n = 57)	61
Poodle (n = 406)	60
Dachshund (n = 1,418)	60

45 Age distribution of dogs with struvite stones in a European study 1999–2001 (n = 1,991).[8]



The majority of struvite stones in dogs occur in the bladder. In male animals, small stones are more common in the urethra; therefore, both the bladder and the urethra can be affected. Struvite stones are rarely found in the upper urinary tract (kidneys, ureters) (*Table 19*).

PATHOGENESIS

Calcium and magnesium phosphate do not dissolve readily in alkaline urine. The monobasic dihydrogen phosphate anion ($H_2PO_4^-$) is present in acidic urine, and forms very soluble salts. As the pH increases, monohydrogen phosphate anions (HPO_4^{2-}) create less soluble calcium salts in weakly acidic urine. However, sufficient free phosphate ions (PO_4^{3-}) are only available at alkaline pH values, allowing the occurrence of struvite stones. The conditions required for the formation of struvite crystals include sufficient magnesium, ammonium, and phosphate concentrations in the urine, but the decisive factor is an alkaline urine pH (**46**).

Table 19 Location of struvite stones in dogs, European study 1999–2001 (n = 1202).[8]

Location	%
Kidney/ureter	0.7
Bladder	72.2
Bladder/urethra	21
Urethra	6.1

The supersaturation of urine with magnesium ammonium phosphate hexahydrate in dogs is generally caused by urinary tract infections with urease-producing bacteria (see *Table 8*, p. 21; **47**). *Staphylococcus* spp. have been most commonly found in dogs, whereas in humans *Proteus* spp. are the predominant agents of urease production. Urea is split by urease (see **11**), causing the urine pH to increase to >7.0. Furthermore, these bacteria metabolize citrate for the production of

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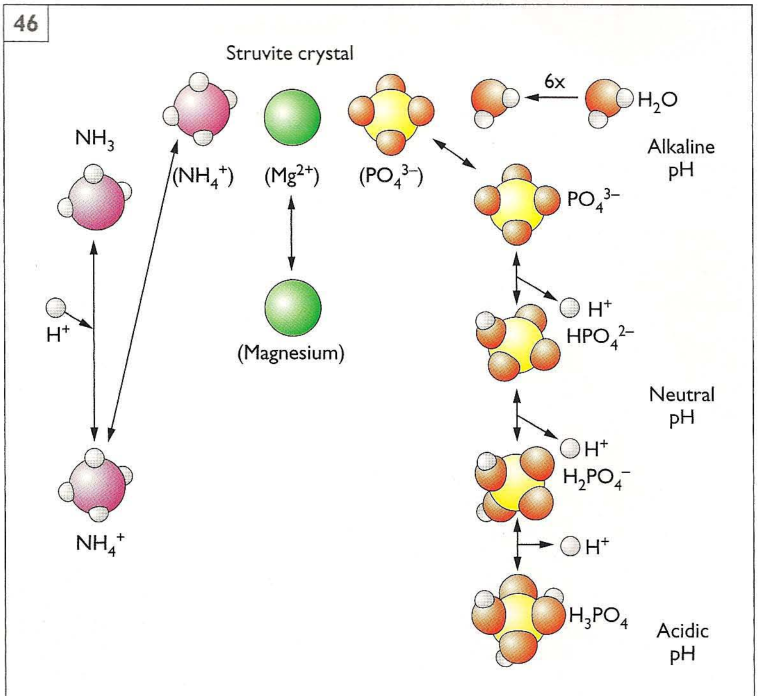


46 Diagrammatic presentation of the occurrence of struvite crystals in urine.

energy thereby dramatically reducing the concentration of citrate in the urine. Citrate is a powerful complexing agent for calcium and magnesium ions and thereby a potent inhibitor of crystallization in urine even in the presence of an infection. This means that other phosphates besides struvite, such as carbonate apatite, can crystallize and serve as mixing partners in the formation of the stones. Infection-induced struvite stones can occur and grow very quickly (2–8 weeks after infection with urease-producing *Staphylococcus* spp.).[135]

Sterile struvite stones have been reported where diets are high in minerals and produce high ammonium concentrations and alkaline urine.[134]

Due to the higher incidence rate in individual dog breeds, a genetic predisposition for struvite stone formation has not been ruled out. For example, recurrent struvite stones were found in three related English Cocker Spaniels with no urinary tract infection, but with an alkaline urine pH.[134]

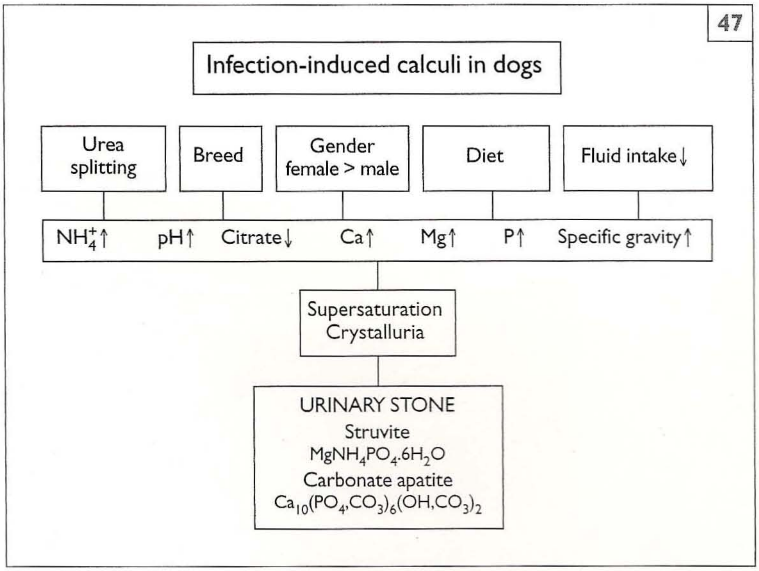
Newberyite ($MgHPO_4 \cdot 3H_2O$) has rarely been diagnosed in dogs with urinary stones. As yet, nothing is known about the exact pathogenesis of this type of stone, but this substance can crystallize in weakly acidic urine at high magnesium concentrations, so a sterile pathogenesis must be assumed.

The prolonged storage of struvite stones ($MgNH_4PO_4 \cdot 6H_2O$) and exposure to warm temperatures can split the water in the crystals leading to the artificial occurrence of dittmarite ($MgNH_4PO_4 \cdot 1H_2O$).[136] Dittmarite is not a true urinary stone but can be seen during the analysis of old stones.

DIAGNOSIS

Urinalysis

- Smell: possibly of ammonia in urinary tract infections.
- Specific gravity: mostly >1.030 (aim: <1.015).
- pH: in urinary tract infections in fasted dogs >7.0.


47
Infection-induced calculi in dogs
Urea splitting
Breed
Gender female > male
Diet
Fluid intake↓
NH_4^+↑
pH↑
Citrate↓
Ca↑
Mg↑
P↑
Specific gravity↑
Supersaturation
Crystalluria
URINARY STONE
Struvite
$MgNH_4PO_4.6H_2O$
Carbonate apatite
$Ca_{10}(PO_4,CO_3)_6(OH,CO_3)_2$

47 Diagram of the pathogenesis of infection-induced struvite stones in dogs.

- Nitrite on dipsticks: not reliable in dogs.
- Bacterial investigation on dipsticks is not reliable in dogs.
- Urine sediment: characteristic coffin-lid-shaped crystals (**29a & b**) (not definite proof of struvite stones!).

In cases of urolithiasis, the urine should be collected under sterile conditions and submitted for culture and antibiotic sensitivity testing. The colony count in the urine sample depends heavily on the withdrawal technique (see *Table 12*, p. 42), urine should be therefore be withdrawn wherever possible using cystocentesis. In dogs with urinary tract infections a single bacterial species is usually present (multiple species often suggest contamination).

Computer programs (EQUIL, SUPERSAT[92;94]) can be used to calculate the risk of occurrence of struvite stones following the quantitative urinalysis.

Blood tests

Signs of inflammation in the blood such as leucocytosis with neutrophilia and a left shift, hyperglobulinaemia or increased acute phase proteins (C-reactive protein, increased erythrocyte sedimentation rate) are usually only found in urinary tract infections due to pyelonephritis. A urinary tract infection of the lower urinary tract, in particular the bladder, does not produce any inflammatory changes in the blood.

Struvite stones only cause serum biochemistry changes if they are in the kidneys and cause subsequent renal failure. Usually the biochemistry is unremarkable.

Diagnostic imaging

Struvite stones are radiopaque and can be clearly seen on survey radiographs (see *Table 13*, p. 45). It is important to image the entire urinary tract and the complete length of the urethra. Struvite stones are round with a smooth surface, often multiple but sometimes solitary and very large (**48**). As with all urinary stones, an ultrasound scan shows a clear hyperechoic area with acoustic shadows that move when the animal changes position.

Urinary stone analysis

If sediment, stone fragments or small stones are flushed out from the urinary tract or the

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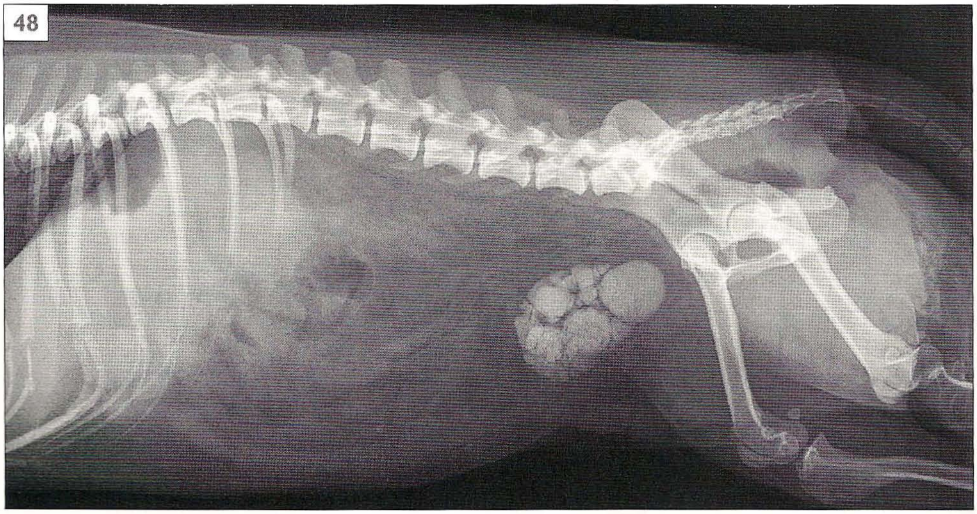

48 Radiograph of a 9-year-old neutered female Pekingese with multiple bladder stones of varying sizes and with smooth surfaces. The stones (100% struvite) were removed surgically, as the dog had problems passing urine.

bladder, or are passed spontaneously, a stone analysis should always be requested. Further therapeutic procedures can then be implemented, as experimental and clinical studies have shown that struvite stones can be dissolved *in vivo*.[137-140] Prophylaxis is only possible if the composition of the stone is known.

Struvite can appear as a mixing partner in all types of urinary stone. As with any case of urolithiasis, a secondary infection may be present. Particular attention should be paid to the accompanying infection in this case, as it is considered to be the primary cause of the urolithiasis.

Test kits for chemical urinary stone analysis are very inaccurate and therefore obsolete.[3,100,141]

Analysis using infrared spectrometry produces reliable qualitative and quantitative results. See Chapter 1, p. 30.

TREATMENT AND LONG-TERM PREVENTION

Treatment

The following measures should be taken in the treatment of dogs with struvite stones in the kidneys or bladder:

- Specific treatment of the urinary tract infection.
- Removal of obstruction if present.
- Abundant fluid therapy to dilute the organisms and reduce the relative supersaturation, in particular the specific gravity of the urine should be brought to <1.015.
- Removal or dissolution of urinary stones.
- Regular monitoring to allow rapid detection of recurrence.

Struvite stones in the ureter or urethra cannot be dissolved as too little urine passes through to produce a conducive environment for this. Other measures must be used in these cases (surgery, urohydropropulsion, endoscopy, lithotripsy). See Chapter 1, pp. 49–52.

Treatment of urinary tract infections

In acute cases treatment of the urinary tract infection can be initiated prior to the results of antibiotic sensitivity testing with a β-lactam antibiotic (ampicillin, amoxicillin–clavulanic acid, cefovecin), a fluoroquinolone (enrofloxacin, marbofloxacin), or trimethoprim sulphonamide. Ideally, culture and sensitivity testing should be performed prior to initiation of treatment, so that the appropriate treatment can subsequently be introduced. A sensitivity test is essential if urinalysis reveals continued infection at the follow-up check and if struvite stones do not decrease in size despite the use of a specific diet and the administration of antibiotics.

The most common bacteria found in dogs with urolithiasis include *Staphylococcus*, *Proteus*, *Escherichia coli*, *Streptococcus*, *Klebsiella*, *Pseudomonas* and *Enterobacter* species.[142,143] In cases of struvite stones, only one species is usually isolated, the most common being the urease-forming *Staphylococcus* spp.[123]

Dietary urinary acidification is not sufficient to dissolve the stones in the presence of urease-producing bacteria. The urine must therefore be kept sterile until undersaturation with stone-forming crystals is achieved. Often viable bacteria can be found within the struvite stones themselves, and these can re-colonize the bladder during stone dissolution. Consequently antibiotic therapy at the full dose should be continued throughout the stone dissolution phase (verified on radiographs or ultrasonography) and then continued for a further 4 weeks after dissolution. However, if the urine is initially sterile the administration of antibiotics can be foregone. If additional diuresis is induced, the antibiotic dose should be adapted to maintain the minimum inhibitory concentration in the diluted urine. Using too low an antibiotic dose or a too short course of antibiotics can lead to the recurrence or renewed growth of bacteria once dissolution has commenced.

The dissolution of struvite stones with antibiotics alone and without a dietary change is rarely possible[66] and is not recommended. Dissolution will take significantly longer (many months) than with a combination of antibiosis and dietary change (several weeks).

The full dose of antibiotics must be administered throughout the period in which the struvite stones are dissolved and for 4 weeks thereafter.

Removal of an obstruction

The removal of struvite stones from the lower urinary tract with surgery or urohydropropulsion (see Chapter 1) is only necessary if they are causing an obstruction (**49**) or if there is a high risk of obstruction and insufficient opportunity to monitor the dog. The surgical removal of struvite stones is further indicated if the bladder lumen is filled with many and/or very large stones, if obstructing urethral stones were flushed into the bladder or if the assumed composition of the stone suggests that dissolution is not possible. Surgical removal of struvite stones from the kidneys (renal calculus) should be weighed against the risk of possible complications (such as intraoperative damage to kidney tissue); however, medical or dietary solutions are not straightforward as the stones cannot be sufficiently exposed to acidic, antibiotic-containing urine. The surgical removal of stones also provides the opportunity of correcting anatomical defects in the urinary tract.

The disadvantages of surgery include those associated with the anaesthesia, hospitalization, aftercare, and so on. There is also a risk of stricture formation with repeated surgical stone removal from the ureters or urethra. It has been shown that struvite stones recur more quickly after surgery than after administration of dietary dissolution.[66] This can probably be accounted for by the fact that not all stones are removed intraoperatively and small stones form the nidus for the formation of new stones.[144]

Dietary measures

A change of diet can be effective on its own for the dissolution of struvite stones. Struvite stone dissolution diets have a relatively low content of high-value protein (15–20%), reduced calcium, magnesium, and phosphorus, and are supplemented with sodium chloride to promote fluid intake.[71] The moderate amounts of protein reduce the production of urea in the liver and thereby the amount of urea in the kidney interstitium and in the urine. There is therefore less urea for bacterial urease. The reduced serum urea in the renal medulla also leads to a reduced concentration gradient,

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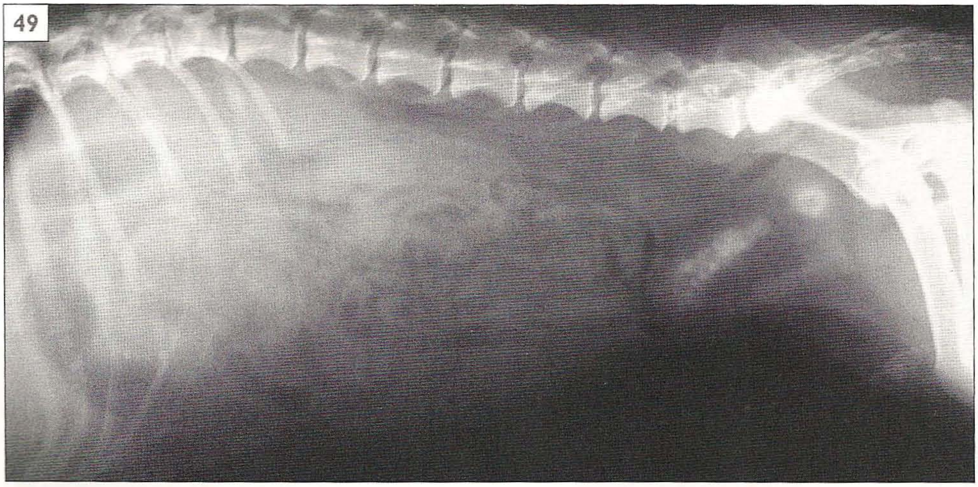


49 Multiple, small stones in the bladder and a somewhat larger stone in the detrusor area of a 6-year-old Dachshund. Due to the presentation of typical coffin-lid-shaped crystals and the urine pH (7.5) together with a urinary tract infection, struvite stones were assumed. The stones were removed surgically as the obstruction made chemolysis impossible. The diagnosis was confirmed following stone analysis (100% struvite).

which in turn leads to the production of less concentrated urine thereby promoting diuresis.

A stone-dissolving diet should only be administered where there is a clear indication, and in the absence of concurrent diseases such as cardiac failure, hypertension, or nephrotic syndrome. In pregnant, lactating, and growing animals, these diets should only be used as short-term measures. A diet with too low a protein content can impair postoperative wound healing. High-fat diets should not be given to animals with altered fat metabolism or with pre-existing pancreatitis, or to Miniature Schnauzers with familial hyperchylomicronaemia.

Stone-dissolving diets should be given until the stones have completely disappeared and for 4 weeks afterwards, so that any very small stones that are no longer visible on radiogaphs or ultrasonography, are eradicated. If not eradicated, these could be a nidus for new stones.

It takes an average 3 months (2 weeks to 7 months) to completely dissolve struvite stones linked to urinary tract infections using dietary measures combined with appropriate antibiotic treatment.[66,145] Sterile struvite stones can be dissolved more quickly (average of 6 weeks; 1–3 months).[146] Dietary stone dissolution should be checked initially after 4 weeks and only be continued if an improvement is seen. Follow-up consultations should then be performed every 4 weeks and should include a history, clinical examination, radiographs, blood tests (urea, albumin, phosphorus), and urinalysis (specific gravity, dipstick, sediment examination, culture, and sensitivity). The serum of dogs on a struvite dissolution diet has reduced levels of urea, phosphorus, and albumin (*Table 20*).[145] Although nutritional studies have shown that this does not present any clinical problems in healthy dogs, such changes demonstrate the unsuitability of such diets in the long term. Reduced urea levels are a good indication of owner compliance.

A struvite dissolution diet should not be used prophylactically or as a long-term maintenance diet. In puppies and pregnant bitches, it should only be used in cases with a strong indication, and for a maximum of several weeks.

Table 20 Comparison of the findings in history, clinical examination, blood tests, and urinalysis before, during, and after struvite stone dissolution.[66]

Finding	Before treatment	During treatment	After successful treatment
Haematuria	- to +++	- after a few days	-
Abnormal urine odour	- to +++	- after a few days	-
Pollakiuria	+ to +++	rarely ↑ later ↓	-
Polyuria	- to +	+ to +++	-
Small urinary stones spontaneously flushed out	Possible	Often (in female dogs)	-
Serum urea	>3.5 mmol/l	0.8–3.5 mmol/l	According to diet
Serum albumin	Normal	↓ by 5–10 g/l	Normal
Serum phosphorus	Normal	Slight reduction	Normal
Urine specific gravity	Variable	±1.004 to ±1.015	Normal
Urine pH	≥7.0	Reduced (acid)	Variable
Urine protein	+ to +++	Reduced to -	-
Struvite crystals	- to +++	Mostly -	Variable
Other crystals	Variable	Variable	Variable
Bacteria in the urine	- to +++	Reduced to -	-
Urine culture	- to +++	Reduced to -	-

Commercial diets that change the urine composition markedly and help in struvite stone dissolution have been developed.

Medical measures

In some countries, acetohydroxamic acid (12.5 mg/kg q12h orally)[147] is licensed for use as an inhibitor of microbial urease in dogs for whom an acid-inducing diet has proved unsuccessful. Acetohydroxamic acid reduces the ammonia content of urine and induces alkalinization, but does not have a significant antibiotic effect. Side-effects include anorexia, vomiting, haemolytic anaemia, and altered bilirubin metabolism.

Amino acid preparations are an effective solution for sterile struvite stones, as they probably lead to acidification of the urine.[148] There are no reports for infection-induced struvite stones.

The medical acidification of urine (e.g. with L-methionine) is not indicated in infection-induced struvite stones, since appropriate antibiotic administration and a special diet are sufficient. In sterile stones this can rarely be used to decrease the pH value to 5.8–6.2.

Difficulties encountered with dissolving stones

As a general rule, large struvite stones take longer to dissolve than smaller ones. Other factors that influence the speed of dissolution of struvite stones include: the number of stones, the location of the stones, and the presence of other components in the stones such as calcium phosphate or calcium oxalate.

The following points should be checked if struvite stones cannot be dissolved:

- Are they really pure struvite stones?
- While the shell of the stone may be struvite, the centre of the stone is not always identical, so after the first successful signs of dissolution, the core does not become smaller.
- A lack of owner or patient compliance with feeding (check blood urea).
- Inadequate antibiotic dose or not given for long enough.
- Antibiotic resistance (urine bacteriology including sensitivity test).

Prevention of recurrence

Successful prevention of recurrence is only possible if all stones have been dissolved and the infection resolved. After stone dissolution, urinary tract infections should therefore be excluded and the urine monitored every 2–3 months in the first year. General prophylactic measures include:

- Clean freely available drinking water.
- Use of wet food, or special prophylactic dry food.
- Check the specific gravity of the urine, aim for <1.020.
- Possible increase in water intake.
- Possible increase in sodium chloride for further diuresis.
- Check the urine pH, aim for 6.2–6.5.

Commercial foods are being developed which will influence the composition of urine for the long-term prevention of struvite stones.

In mixed stones, a genetic anomaly such as cystine, urate or xanthine excretion may be the predisposing factor for stone occurrence.

It is rarely necessary to administer long-term antibiotic treatment in dogs with persistent urinary tract infections. Predisposing factors for urinary tract infections should also be treated (diabetes, hyperadrenocorticism, urachal diverticula).

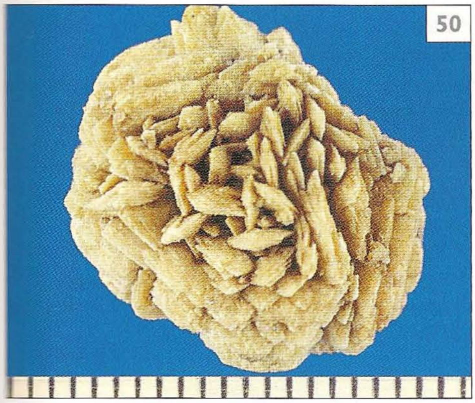
Calcium oxalate stones

INTRODUCTION

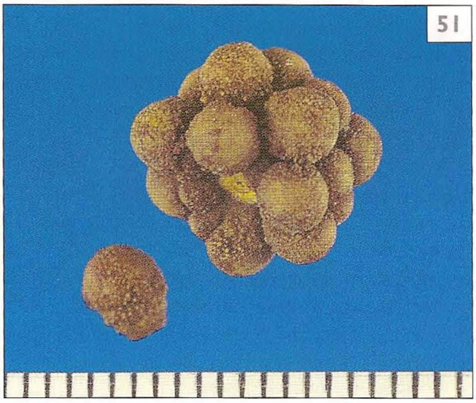
Calcium oxalate urinary stones can occur in two different mineralogical phases (**50, 51**), which can only be differentiated by the water content of the crystal. *Calcium oxalate dihydrate* (weddellite) is tetragonal and produces typical envelope-shaped crystals in urine sediment (**52**, see also **29**). Weddellite stones are primarily composed of well formed, hard, individual crystals with an irregular surface. In urine sediment, weddellite crystals are almost colourless and the stones they form are yellow to brown. Weddellite is unstable as a pure chemical compound and restores itself to calcium oxalate monohydrate (whewellite) when a molecule of water of crystallization is removed. This means that weddellite can be stabilized in urine containing substances such as magnesium and calcium.[149] The conversion from weddellite into whewellite can occur in a urinary stone inside the body (pseudomorphism, see **15**). The occurrence of weddellite stones is most commonly associated with hypercalciuria.

Calcium oxalate monohydrate (whewellite) is monoclinic and the crystals present a variety of shapes in urine sediment – dumbbell, ellipsoid, or long oval shaped (**53**). Whewellite stones are microcrystalline, very compact, hard and brown to black in colour. The surface is mostly smooth to rough and commonly has mulberry-shaped protrusions (**51**). It has been shown that the occurrence of whewellite stones is often linked to hyperoxaluria.[149,150] Only whewellite stones are found in primary hyperoxaluria and they may also be seen with excessive urinary oxalate excretion. In a study of the analysis of urinary stones in dogs in Europe, pure weddellite stones (20%) were more common than pure whewellite stones (5%).[8] Weddellite stones grow quicker than whewellite stones and recurrence is more common. Contrary to the findings in Europe, more whewellite (44.7%) than weddellite (6.8%) stones were found in dogs in the USA.[7]

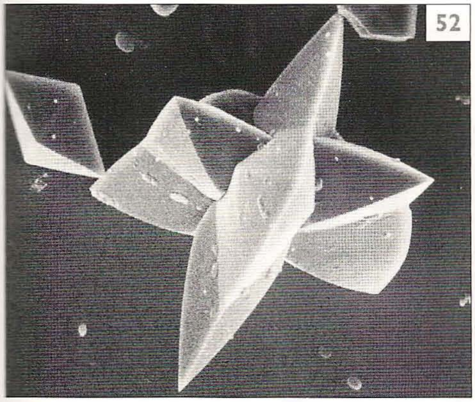
Mixed calcium oxalate stones usually contain carbonate apatite, as well as the two calcium oxalates.



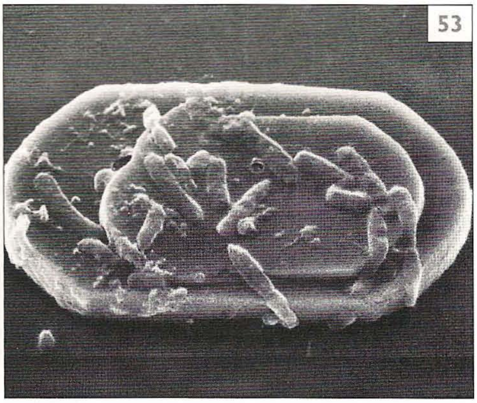
50 Weddellite – urinary stone in a dog with well developed, sharp-edged crystals on the surface.



51 Whewellite – spherical urinary stones in a dog.



52 Weddellite – twin crystal in urine sediment, scanning electron microscopic image.



53 Whewellite – long oval crystal in urine sediment with adherent bacteria, scanning electron microscopic image.

EPIDEMIOLOGY

In large studies from the 1970s and 80s, calcium oxalate stones in dogs were relatively rare:

- Great Britain – 1970 0%.[151]
- USA – 1977 3%,[152] 1981 5%.[28]
- Germany – 1981 1.3%,[153] 1986 7%.[33,106]

Since the 1980s there has been a continual increase in the frequency of calcium oxalate stones in dogs in the USA and Europe (**54**). A Canadian study from 1998–2003 reports 41.5% calcium oxalate stones.[24] In the Benelux countries, the frequency of calcium oxalate stones rose from 33% in 1994 to 46% in 2003.[24a]

A marked increase in calcium oxalate stones was reported between 1981 and 1998 in male dogs, but this was less marked in female animals. Trend calculations into the frequency of struvite and calcium oxalate stones in dogs in the USA confirm that a plateau was reached in 1998–2001.[154]

A European study in 1999–2001 examined 4,082 urinary stones from dogs from 27 countries, 32.3% of which were calcium oxalate stones. It is notable that in the individual countries, the percentage share of calcium oxalate stones fluctuated between 16 and 59% (*Table 21*). This can presumably be traced back to different breed distributions in each country.

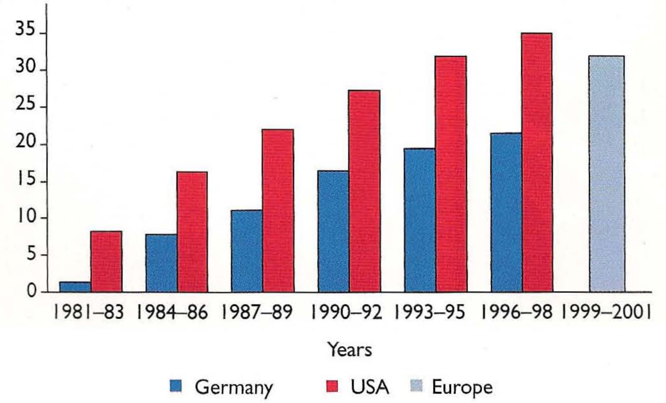
A marked breed predisposition has been demonstrated in dogs for the occurrence of calcium oxalate stones. Some breeds were never affected such as the Bernese Mountain Dog and Bull Terrier, in others only a few calcium oxalate stones were diagnosed (Rottweiler 1%, Bassett 1%, Dalmatian 1%), whilst some breeds showed a marked predisposition (*Table 22*).

The frequency of calcium oxalate stones in small dog breeds such as Miniature Schnauzers and Yorkshire Terriers has also been reported by other authors.[7,23,24,24a] Similarly to humans, an increased risk of calcium oxalate stone formation in dogs is associated with obesity.[6,155] In addition to breed, male animals have a very marked predisposition for calcium oxalate stones (**55**). A high incidence of calcium oxalate stones in male animals was also confirmed in studies from other countries (*Table 23*).

Almost 90% of all calcium oxalate stones are found in male animals.[8]

The average age of dogs with calcium oxalate stones is between 8 and 8.5 years (range <1–18 years), i.e. calcium oxalate stones are a disease of older animals. Over 76% of dogs with calcium oxalate stones are older than 7 years (**56**).

54



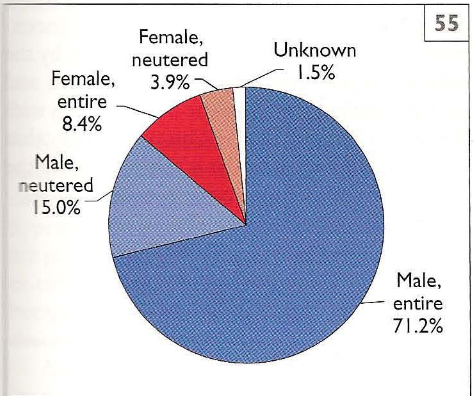
54 Percentage frequency of calcium oxalate stones in dogs from different regions and time periods.[7,8,111,153]

Table 21 Frequency distribution of calcium oxalate stones in different European countries in 1999–2001; 4,082 urinary stones, 1,318 calcium oxalate stones (32.3%).[8]

Country (number of stones)	Calcium oxalate (%)
Finland (n = 392)	59.4
Switzerland (n = 137)	43.8
Holland (n = 364)	43.4
Italy (n = 429)	40.1
France (n = 270)	34.8
Germany (n = 1,787)	21.3
Austria (n = 50)	16.0

Table 22 Dog breeds in which calcium oxalate stones predominantly occur (total number of stones n = 7,697).[10]

Breed (number of stones)	Share of calcium oxalate stones (%)
Welsh Terrier (n = 57)	72
Fox Terrier (n = 88)	69
Dobermann (n = 64)	52
Cairn Terrier (n = 51)	39
Yorkshire Terrier (n = 800)	35
Miniature Schnauzer (n = 141)	33
Lhasa Apso (n = 57)	33
West Highland White Terrier (n = 169)	30

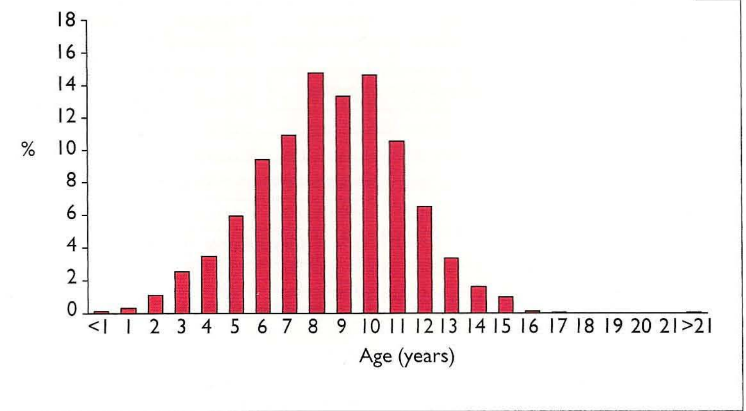


55 Sex distribution of dogs with calcium oxalate stones, European study 1999–2001 (total number n = 4,082, calcium oxalate stones n = 1,318).[8]

Table 23 Sex distribution of dogs with calcium oxalate stones in different countries.[10,23,24,28]

Country	Ratio female:male
Canada	1:3
USA	1:2.6
Czech Republic	1:5.8
Germany	1:8.3

56 Age distribution of dogs with calcium oxalate stones in a European study 1999–2001 (n = 1,318).[8]



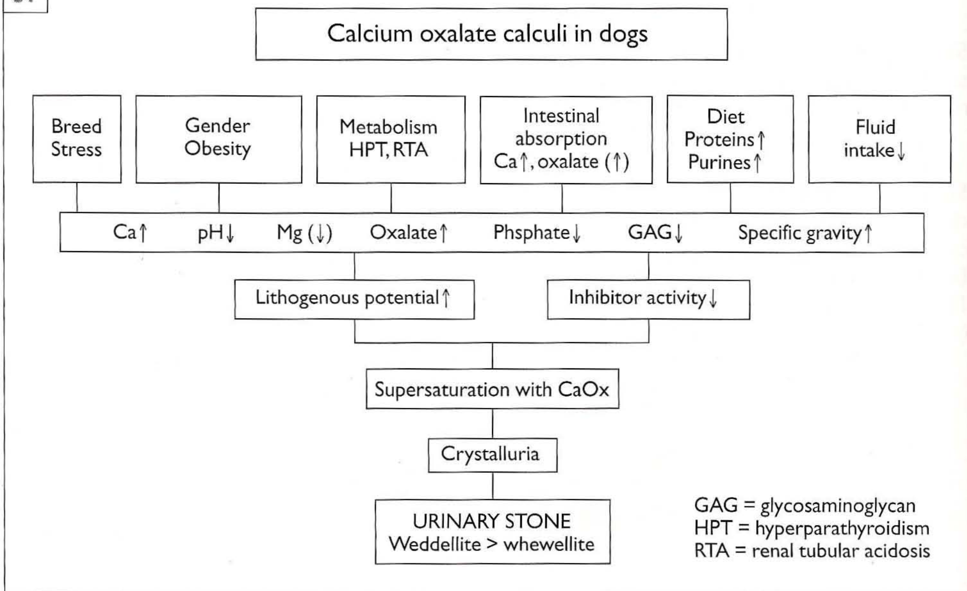
In dogs, calcium oxalate stones are mostly found in the bladder. Due to the higher incidence of this type of stone in male animals (**55**), the stones can obstruct the lower urinary tract, therefore in over 50% of cases the urethra is also affected (*Table 24*).

PATHOGENESIS

The higher incidence of calcium oxalate stones in male dogs of smaller breeds clearly indicates that specific relationship patterns, metabolic processes, and anatomical considerations all play a role in the development of the disease, thus disproving the long-held theory that diet was the only predisposing factor (**57**). The analysis of urine in healthy Miniature Schnauzers in comparison with healthy Labrador Retrievers under the same conditions, revealed a significantly increased relative supersaturation of urine with brushite in the Miniature Schnauzers but not with calcium oxalate.[156] The Miniature Schnauzers had a higher concentration of calcium, but a lower urinary oxalate concentration than the Labrador Retrievers. Comparable findings (higher calcium and lower oxalate) were also found in Miniature Schnauzers with urinary stones in comparison with healthy Beagles.[157] A comparison of urinalysis results from dogs with urinary stones from different breeds, sexes, and ages showed a relative supersaturation of the urine with calcium oxalate, with high calcium and oxalate concentrations and lower phosphate and potassium concentrations.[158,159] Laboratory investigations by the author (Hesse), revealed higher calcium and oxalate concentrations in the urine of dogs with stones (*Table 25*). This shows that hypercalciuria in particular is responsible for the occurrence of calcium oxalate stones in dogs.

Table 24 Location of calcium oxalate stones in dogs, European study 1999–2001 (n = 741).[8]

Location	%
Kidney/ureter	0.8
Bladder	44.1
Bladder/urethra	32.8
Urethra	22.3


Calcium oxalate calculi in dogs
Breed Stress
Gender Obesity
Metabolism HPT, RTA
Intestinal absorption Ca↑, oxalate (↑)
Diet Proteins↑ Purines↑
Fluid intake↓
Ca↑
pH↓
Mg (↓)
Oxalate↑
Phsphate↓
GAG↓
Specific gravity↑
Lithogenous potential↑
Inhibitor activity↓
Supersaturation with CaOx
Crystalluria
URINARY STONE Weddellite > whewellite
GAG = glycosaminoglycan
HPT = hyperparathyroidism
RTA = renal tubular acidosis

57 Diagram of the pathogenesis of calcium oxalate stones in dogs.

Table 25 Results of quantitative urinalysis in dogs with calcium oxalate stones and in healthy dogs (mean ± SEM), *$p \leq 0.05$).[8,38]

Analyte	Healthy dogs	Dogs with calcium oxalate stones
Sodium (mmol/l)	121.3 ± 6.7 (n = 132)	94.7 ± 5.7 (n = 122)*
Potassium (mmol/l)	96.1 ± 4.5 (n = 132)	78.4 ± 4.9 (n = 122)*
Calcium (mmol/l)	1.49 ± 0.10 (n = 134)	2.15 ± 0.12 (n = 128)
Magnesium (mmol/l)	3.28 ± 0.20 (n = 134)	3.38 ± 0.24 (n = 127)
Sulphate (mmol/l)	30.1 ± 1.40 (n = 132)	26.4 ± 1.82 (n = 124)*
Phosphate (mmol/l)	39.4 ± 1.75 (n = 134)	36.4 ± 2.42 (n = 128)*
Citrate (mmol/l)	0.438 ± 0.04 (n = 134)	0.636 ± 0.07 (n = 99)*
Oxalate (mmol/l)	0.766 ± 0.03 (n = 134)	0.847 ± 0.04 (n = 128)
Uric acid (mmol/l)	0.78 ± 0.04 (n = 134)	0.61 ± 0.04 (n = 127)*
Creatinine (mmol/l)	12.4 ± 0.55 (n = 134)	10.0 ± 0.57 (n = 128)*
Protein (mg/l)	560.7 ± 63.1 (n = 134)	1027.9 ± 96.8 (n = 127)*

Systemic diseases that induce increased calcium excretion in the urine can be seen as a cause; hypercalcaemia caused by primary hyperparathyroidism and hyperadrenocorticism are possible.[125,160] Distal renal tubular acidosis or other causes of hypercalcaemia have not yet been described as causative in dogs, but they are theoretically possible.

A genetic predisposition cannot be ruled out in specific breeds in which calcium oxalate stones are common.[161] A familial increase in hypercalciuria has been proven in human medicine.[162,163] Genetic studies have not been conducted dogs and only rarely in humans.[61,62]

In humans a positive link has been found between sodium chloride intake (100–300 mg/kg/day) and an increase in urinary calcium excretion.[164,165] However, studies in healthy dogs demonstrated that an intake of 170–230 mg NaCl/kg/day increased urine sodium concentration, but decreased the calcium concentration as the urine volume increased.[159,166,167] Under these conditions, the relative supersaturation of calcium oxalate was also reduced, therefore a long-term prophylactic effect can be expected with the specific addition of sodium chloride (0.9–1.2%) to wet food. There are still no long-term studies into the effect of comparable sodium chloride amounts on metabolism. Epidemiological investigations have however shown that dogs on high-calcium diets have fewer calcium oxalate stones.[168]

As yet, there have been no veterinary medical investigations into the role of the supplementation and intestinal absorption of oxalate regarding the occurrence of calcium oxalate stones. In humans, increased oxalate absorption is diagnosed in over 45% of people suffering with stones.[169] Oxalate absorption is inversely related to calcium supply.[170]

Up to now the role of *Oxalobacter formigenes* as an oxalate-reducing bacteria in the intestinal tract in dogs has not been documented. In humans there is an association with calcium oxalate urolithiasis, and by introducing these bacteria, urinary oxalate excretion can be reduced.[172] Little is known about the role of high molecular weight substances in the urine (Tamm-Horsfall mucoprotein, prothrombin, nephrocalcin, glycosaminoglycan, bikunin) in dogs; these molecules have been found to be related to the occurrence of calcium oxalate stones in humans. Glycosaminoglycans, for example, can inhibit calcium oxalate crystallization.[173] Initial measurements in dog urine have shown lower (not significant) glycosaminoglycan concentrations in dogs with calcium oxalate stones in comparison to healthy dogs.[8] Also, dogs with calcium oxalate stones have altered nephrocalcin fractions in comparison with healthy Beagles.[168]

As with any other type of stone, supersaturated urine is a prerequisite for the formation of calcium oxalate stones. This is almost always the case for calcium oxalate, and it is only due to the presence of inhibitors (magnesium, citrate) that a wide metastable zone exists (see **14**), in which crystal formation is not inevitable. The relative calcium oxalate supersaturation as a measure of the risk of stone formation can be calculated from quantitative urinalysis using specialist computer programs (EQUIL, SUPERSAT).[92,94,159,167]

DIAGNOSIS

There is a high recurrence rate of calcium oxalate stones at over 36% within a year[174] and up to 60% within 3 years.[175] After stone removal an accurate work-up is therefore essential for successful prophylactic management.

Urinalysis

- Specific gravity: commonly >1.030.
- pH: fasting value commonly <6.0.
- Microbiology (secondary urinary tract infections can occur with calcium oxalate stones).
- Crystalline urine sediment: weddellite and whewellite crystals (**29**; *Table 11*, p. 39) (not definite proof of calcium oxalate stones!).
- Possible fractional electrolyte excretion of calcium, phosphorus, and quantitative analysis of oxalate and citrate (*Table 25*).
- The EQUIL or SUPERSAT computer programs can be used to determine the relative supersaturation as a measure of the risk of urinary stone occurrence.[92,94,159,167]

Blood tests

Calcium oxalate stones do not lead to any haematological or biochemical changes, unless they are bilateral in the kidneys or ureters and lead to renal failure.

To establish blood calcium levels, ionized calcium should be measured, and when measuring the overall calcium, the albumin concentration in the serum should also be considered. In the presence of hypercalcaemia, parathyroid hormone (PTH) and parathyroid hormone-like protein (PTH-rP) levels should be determined. To do this plasma should either be frozen or sent to a laboratory in a protease inhibitor stabilization tube to determine the PTH and PTH-rP.

Hypercalcaemia can lead to increased renal calcium excretion.[125]

Diagnostic imaging

Calcium oxalate stones are radiopaque and are easier to visualize, both in the kidneys and the lower urinary tract, on plain radiographs than on contrast radiographs (see *Table 13*, p. 45). They can have either smooth or very irregular surfaces. As always, the entire urinary tract should be viewed in both projections (lateral and ventrodorsal), otherwise stones can easily be overlooked (**58**). Ultrasound imaging can be used to reveal tiny stones in the urinary tract due to their typical acoustic shadows.

Urinary stone analysis

Calcium oxalate stones are usually small and multiple (*Tables 26, 27*). It is therefore important that all stones are removed and sent for analysis.

The majority of calcium oxalate stones are a mixture of both calcium oxalate phases – whewellite and weddellite. Carbonate apatite is also often present. Less commonly, brushite, cystine, or struvite are found in calcium oxalate stones.

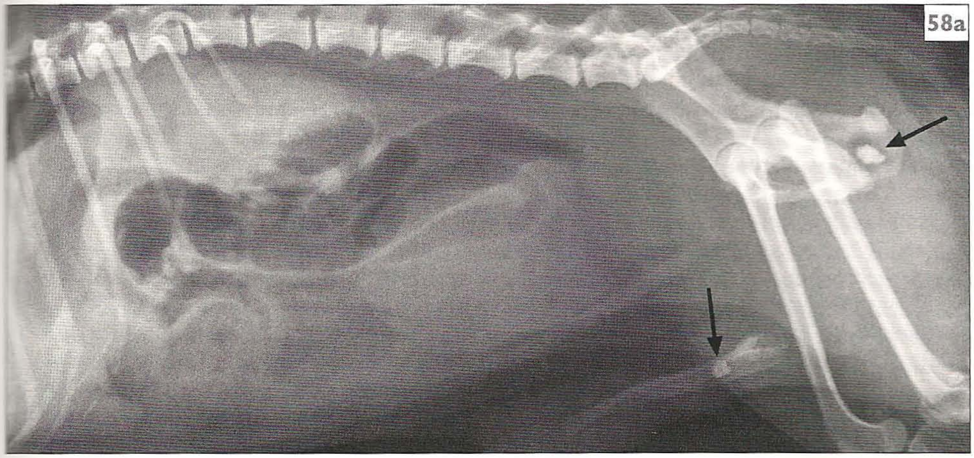
Chemical urinary stone analysis using test kits is very inaccurate and is therefore obsolete.[3,100,141]

Analysis using infrared spectrometry produces definite qualitative results.[100] See Chapter 1, p. 30.

TREATMENT AND LONG-TERM PREVENTION

Various measures should be introduced in the treatment of calcium oxalate stones:

- Removal of obstructions if necessary.
- Administration of abundant fluid therapy to reduce the relative supersaturation; aim for a specific gravity of <1.020.
- Treatment of potential risk factors (hyperparathyroidism, hyperadrenocorticism).
- Removal of the urinary stones if clinically indicated.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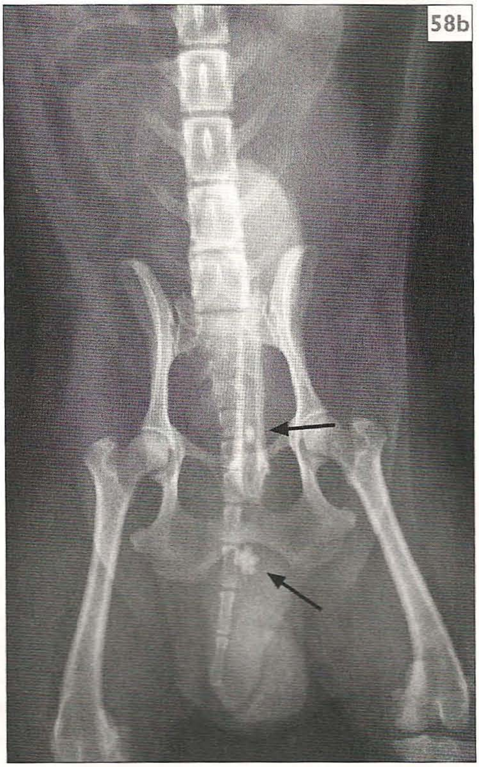
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58 (**a**) Lateral radiograph of an 11-year-old male Yorkshire Terrier with two irregularly shaped urinary stones in the urethra, one above the pelvic floor and one above the os penis (arrows). Following surgical removal, the stones were analysed as being 95% whewellite.
(**b**) Ventrodorsal radiograph of the same dog. The irregular calcium oxalate stone in the urethra can be seen more clearly on this view.

Table 26 Number of calcium oxalate stones in dogs (n = 576).[8]

Number of stones	%
1	26.4
2	12.7
3	8.9
4	6.6
5	5.9
6–19	28.4
≥20	11.1

Table 27 Weight of calcium oxalate stones in dogs (n = 591).[8]

Stone weight	%
<0.01 g	10.5
0.01–1.0 g	78.8
>1.0 g	10.7

- Prevent recurrence with regular monitoring (*Table 28*) and an appropriate prophylactic diet.

Treatment

- Calcium oxalate stones cannot be dissolved.
- Small stones can be removed using urohydropropulsion.
- Large symptomatic stones should be removed either surgically or endoscopically.
- Calcium oxalate stones should be removed immediately if they are causing an obstruction.
- It is important that all stones are removed so that no nidus exists to create a recurrence.

Prevention

Dietary measures

- Abundant fluid therapy, aim for a specific gravity of <1.020.
- The use of commercial dry food is associated with an increased risk of stone formation.[70]
- The ideal protein intake is hard to determine as initially reduced protein is desirable as it should lead to a decrease in acidic valence and calcium excretion in urine;[174] however recent observations show a higher protein content lowers the risk of calcium oxalate.[70]
- A weakly acidic urine pH of 6.2–6.5 through the restriction of animal proteins is desirable. Whereas excessive acidification (pH <6.0) can increase urinary calcium content through metabolic acidosis and encourages the formation of calcium oxalate stones, a high pH value (>6.8) can lead to the formation of struvite and calcium phosphate stones.
- While the excessive addition of sodium chloride (0.8 g/100 kcal) leads to increased calcium excretion, which has been observed in dogs with calcium oxalate stones, it has also been shown that low dietary sodium chloride increases the risk of calcium oxalate stones (an increase in NaCl from 0.06 g/100 kcal to 0.3 g/100 kcal significantly reduced calcium oxalate 'relative supersaturation')[167]. The volume of urine was increased by adding controlled amounts of sodium chloride.[166,176]
- Sufficient, but not excessive, addition of calcium to encourage intestinal binding of oxalate[170] (see calcium content of food – Appendix, pp. 143–4).
- No food with a high oxalate content (see Appendix, pp. 145, 146).
- High fibre, vegetable-orientated diet.
- No vitamin C supplements.

Table 28 Evaluation of findings in history, clinical investigations, blood, and urinalysis before and during calcium oxalate stone prophylaxis.

Finding	Before prophylaxis	During prophylaxis
Haematuria	- to +++	- after a few days
Pollakiuria	+ to +++	-
Polyuria	- to +	Variable
Small urinary stones spontaneously flushed out	Possible	Hardly
Serum urea	>3.5 mmol/l	<3.5 mmol/l
Urine specific gravity	Variable	±1.004 to ±1.015
Urine pH	<6.0	<7.0
Urine protein	+ to +++	Reduced to -
Calcium oxalate crystals	- to +++	-
Other crystals	Variable	-
Bacteria in the urine	- to +++	-
Urine culture	- to +++	-

Commercial foods have been developed that effectively reduce calcium oxalate recurrence in the composition of urine.

Pharmacological measures

Should calcium oxalate crystalluria persist or if recurrent calcium oxalate stones appear, medical prophylaxis may be considered:

- Alkalinization of the urine: alkaline citrate increases the urine pH to 6.5–6.8. This does not increase citrate excretion in dogs,[177] but the increase in urine pH is prophylactic (excessive alkalinization can increase the risk for struvite stone formation). Potassium citrate is recommended at a dose of 50–75 mg/kg/day mixed with food. Sodium bicarbonate is less effective and can cause hypercalcuria.
- Reduced calciuresis: hydrochlorothiazide (2–4 mg/kg q12h orally) reduces renal calcium excretion,[178] most likely due to volume reduction leading to increased reabsorption of solutes (e.g. calcium) in the proximal tubule. This effect is not seen with chlorothiazide.[179] There are no long-term studies into the use of hydrochlorothiazide and there is a risk of dehydration, hypokalaemia, and hypercalcaemia. It is therefore important to monitor serum electrolyte values regularly (every 2–4 weeks).

A urinary tract infection should be excluded in all cases with calcium oxalate stone formation.

Monitoring

As small calcium oxalate stones can be removed from the bladder using urohydropropulsion, at-risk patients should be monitored every 4–6 months with radiography or ultrasound examination.

Calcium phosphate: carbonate apatite stones

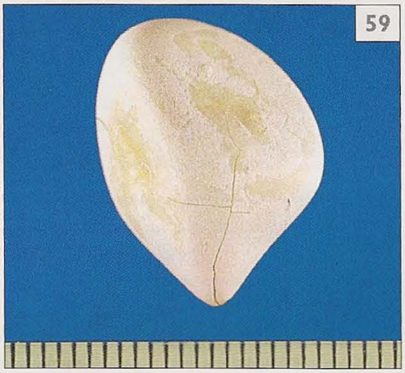
Different types of calcium phosphate stones have been found in dogs:[23,24,28]

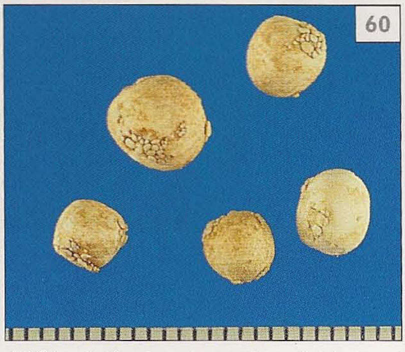
- Tricalcium phosphate (whitlockite), $Ca_3(PO_4)_2$.
- Hydroxyapatite (calcium hydroxyphosphate), $Ca_5(PO_4)_3OH$.
- Carbonate apatite (hydroxyapatite containing carbon), $Ca_{10}(PO_4,CO_3)_6(OH,CO_3)_2$.
- Brushite (calcium hydrogen phosphate dihydrate), $CaHPO_4 \cdot 2\ H_2O$.

The analytical differentiation of the first three calcium phosphates is highly dependent on the method used (infrared spectrometry, x-ray diffraction, or polarization microscopy). Not all mentioned methods are capable of distinguishing between these three phosphates, but all three stones contain tertiary calcium phosphate, so their pathogenesis can be considered as being identical. From knowledge acquired in human medicine, all calcium phosphate urinary stones have a stored share of carbonate ions,[103,180,181] which can be demonstrated definitively using infrared spectrometry of carbonate. Thus the first three types of stones are usually referred to as carbonate apatite.

INTRODUCTION

Carbonate apatite is typically found in association with struvite and calcium oxalate stones (**59, 60**).


59 Struvite/carbonate apatite mixed stone.


60 Struvite/carbonate apatite mixed stones.

Pure carbonate apatite stones are rare in dogs. Their external appearance can be confused with struvite stones. The colour is white to grey and the surface is microcrystalline to pseudomorphic; there are no well formed carbonate apatite crystals. They are relatively friable.

EPIDEMIOLOGY

The frequency of carbonate apatite stones lies between 0.5 and 3.0% (*Table 29*). Carbonate apatite stones have been found in over 40 breeds. Predominantly affected breeds are the Cocker Spaniel, Cairn Terrier, Yorkshire Terrier, Shih Tzu, Miniature Schnauzer, and Poodles.[8,28] The average age of dogs with carbonate apatite stones is 7 years (range: 1 month to 16 years).[28]

PATHOGENESIS

Carbonate apatite is frequently found as an admixture with calcium oxalate stones (whewellite and weddellite). When carbonate apatite comprises less than 20% of the stone's composition it is considered as a secondary finding. Circadian rhythms and postprandial increases in urine pH create ideal conditions (61) for the precipitation and storage of carbonate apatite in calcium oxalate stones. In dogs, postprandial pH values have been measured at >7.5.[156]

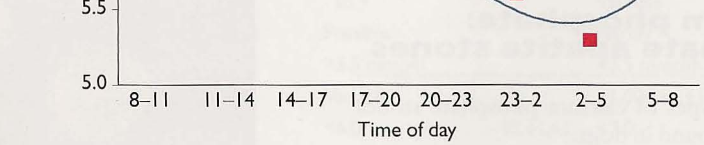
Hypercalciuria reduces the solubility of calcium phosphate and can thereby lead to supersaturation of the urine. Possible causes of hypercalciuria are increased bone resorption, increased calcium absorption by the intestinal tract, reduced calcium resorption in the renal tubule, or a combination of all these factors.

In humans, calcium phosphate crystal inhibitors are known which form chelates with stone components, thereby suppressing the occurrence and growth of calcium phosphate stones. Examples of such substances include inorganic pyrophosphates, citrate, magnesium ions, and nephrocalcin.[182]

Higher concentrations (>20%) of carbonate apatite in a calcium oxalate stone could be due to the increased excretion of calcium in the urine; further diagnostic measures and treatment should therefore be considered.

The conditions required for carbonate apatite incorporation in struvite stones are similar. Small amounts of carbonate apatite are insignificant but large amounts should be monitored. At urine pH values of >7.0,

61

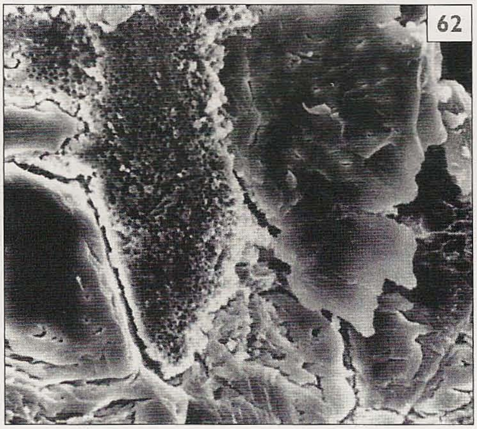


61 Circadian rhythms in human urine pH.

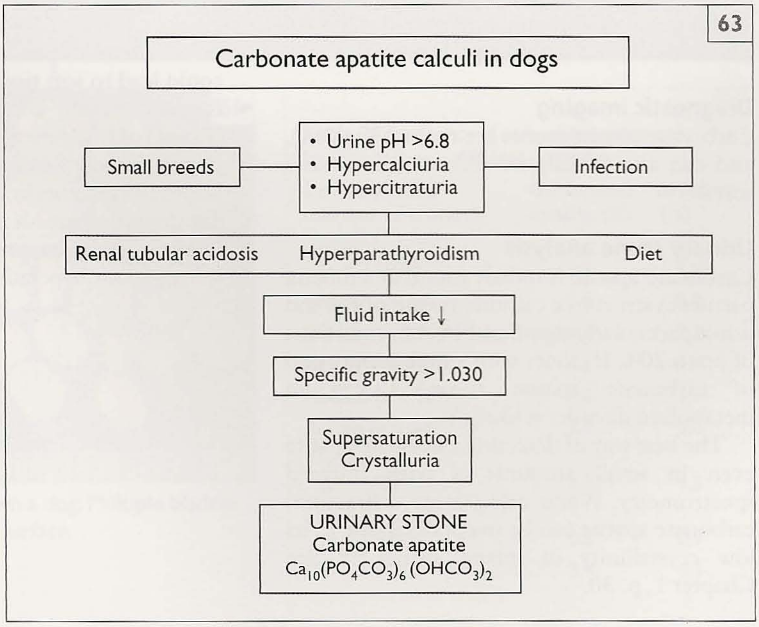
carbonate apatite and struvite do not dissolve readily and both can precipitate out. The presence of carbonate apatite is not usually linked to an infection, but the alkaline urine pH in urinary tract infections can promote precipitation. Calcification and bacteria may sometimes be seen in the carbonate apatite as 'footprints' after atrophy (**62**).[106]

If pure carbonate apatite stones are found in a dog, impaired calcium metabolism due to primary hyperparathyroidism or hyperadrenocorticism (**63**) should be considered.[125,183] In humans, various conditions involving abnormal calcium metabolism have been described as causes (malignancy-induced hypercalcaemia, granulomatous diseases, vitamin D poisoning, excessive calcium intake), as well as distal renal tubular acidosis. In dogs, however, such diseases have not been associated with the occurrence of carbonate apatite stones.

62 Scanning electron microscope image of struvite stones in a dog: compact struvite crystals and pseudomorphic carbonate apatite storage with clear 'bacterial footprints'.



63 Diagram of the pathogenesis of carbonate apatite stones in dogs.


Carbonate apatite calculi in dogs
Small breeds
• Urine pH >6.8
• Hypercalciuria
• Hypercitraturia
Infection
Renal tubular acidosis
Hyperparathyroidism
Diet
Fluid intake ↓
Specific gravity >1.030
Supersaturation
Crystalluria
URINARY STONE
Carbonate apatite
$Ca_{10}(PO_4CO_3)_6(OHCO_3)_2$

DIAGNOSIS

Urinalysis

- Specific gravity: mostly >1.030.
- pH: mostly >6.8.
- No characteristic crystals in urine sediment, pseudomorphic.

Bacteriology should always be performed. In the event of primary hyperparathyroidism or distal renal tubular acidosis, and when carbonate apatite is found secondary to calcium oxalate stones, the urine is usually sterile. However, in cases with mixed carbonate apatite and struvite stones, an infection is usually the primary cause.

Analysis of the fractional excretion of calcium and citrate will demonstrate hypercalciuria and hypocitraturia.

Blood tests

Carbonate apatite stones do not lead to any haematological or biochemical changes unless the condition is bilateral in the kidneys or ureters with resulting renal failure.

If hypercalcaemia is present, a PTH assay should be performed to exclude primary hyperparathyroidism.

> Measure the total calcium or ideally the ionized calcium in serum if pure carbonate apatite stones are present.

Blood gas analysis should be performed if distal renal tubular acidosis is suspected.

Diagnostic imaging

Carbonate apatite stones are radiopaque (**64**), and can also usually be seen on ultrasound scans.

Urinary stone analysis

Carbonate apatite is mostly found as a mixing partner in struvite or calcium oxalate stones and is not particularly significant in concentrations of up to 20%. If stones with a high proportion of carbonate apatite recur, a calcium metabolism disorder is likely.

The best way of detecting carbonate apatite even in small amounts is with infrared spectrometry. When using x-ray diffraction, carbonate apatite can be overlooked due to its low crystallinity in mixed stones.[100] See Chapter 1, p. 30.

TREATMENT AND PREVENTION

Treatment

- Spontaneous voiding rarely occurs (small stones).
- Asymptomatic stones (incidental finding) do not need to be removed.
- Dissolution of stones mixed with struvite is possible (see Struvite stones).
- Small stones in the bladder can be removed via urohydropropulsion.
- Dissolution is not possible for stones mixed with calcium oxalate; symptomatic stones should therefore be removed surgically.

Prevention

- Achieving the highest possible volume of urine with a low specific gravity (<1.020) through a special diet. A low-protein wet food can be used to reduce the urea content in the renal interstitium.
- Monitoring for infection.
- Medications that induce calciuresis should be avoided (glucocorticoids, furosemide, acetazolamide).
- The urine can be acidified in cases of pure carbonate apatite stones (e.g. with L-methionine or by diet), pH <6.5.
- If hypercalciuria is diagnosed, thiazide diuretics (2–4 mg/kg orally, twice daily) can lead to reduced excretion of calcium via the kidneys. This treatment should not be used in absorptive hypercalciuria as it could lead to soft tissue calcification.
- Regular (initially after 2–4 weeks) urine checks (pH, sediment).
- Regular (every 3–6 months) radiographic or ultrasound checks.
- Treatment of any identified primary cause (surgery for hyperparathyroidism,[184] trilostane for hyperadrenocorticism[185]).

Calcium phosphate: brushite stones

INTRODUCTION

Brushite stones are rare. They appear mostly as a pure mineral or in mixtures with calcium oxalate dihydrate (weddellite) or carbonate apatite. The structure is very strong so they are quite resistant to fragmentation using lithotripsy. The surface of the stone can be smooth (**65**) and formed of microcrystals, but a coarse crystalline structure can also occur.

EPIDEMIOLOGY

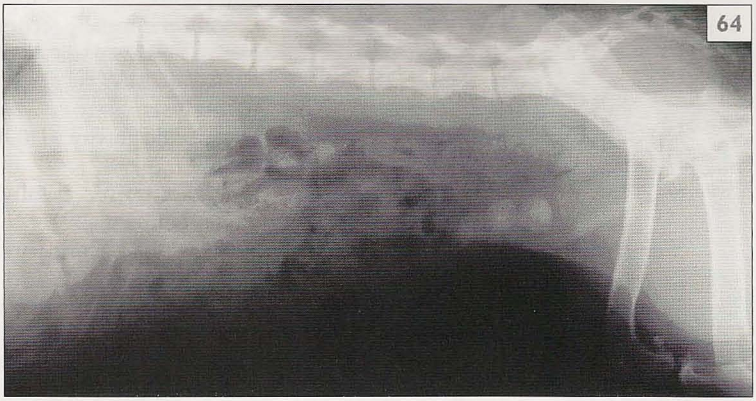
The frequency of brushite stones from different studies and countries lies between 0.5 and 2.0% (*Table 29*).

Brushite stones are predominantly diagnosed in specific breeds, e.g. Yorkshire Terrier, Poodle, Shih Tzu, Schnauzer, Bichon Frisé, and Cairn Terrier.[8,28] Overall, brushite stones were found in over 25 dog breeds, which were mostly small dogs. The Dachshund, which is one of the most common breeds in Germany, is very rarely diagnosed with brushite stones.

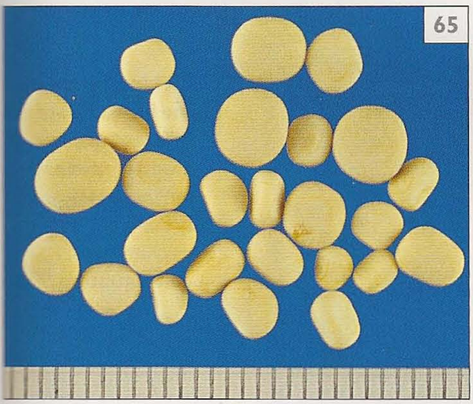
The average age of dogs with brushite stones was 7 years (range: 1 month to 16 years). Male dogs were affected much more (75–83%) than female dogs (17–25%).[28,183]

PATHOGENESIS

Brushite is an acidic calcium phosphate ($CaHPO_4.2H_2O$); it forms in acidic urine at a pH below 6.5 and with appropriately high



64 Multiple mixed carbonate apatite stones in a 3-year-old female crossbreed. The dog had a previous history of urinary stones. Analysis showed calcium oxalate to be involved.



65 Brushite stones from a dog. Multiple bladder stones with a smooth surface.

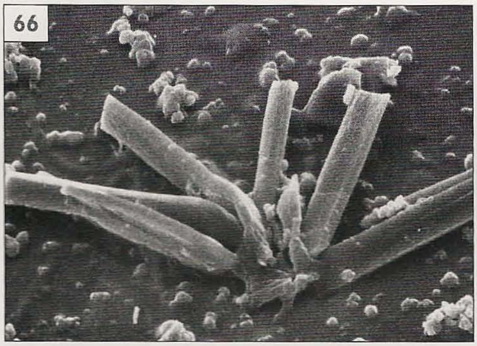
Table 29 Frequency of carbonate apatite and brushite stones in different countries.

Country (total number of stones)	Carbonate apatite (%)	Brushite (%)
Germany (n = 7,697)[8,111]	1.2	1.5
Finland (n = 392)[8,111]	1.5	0.8
France (n = 270)[8,111]	0.7	2.2
Italy (n = 429)[8,111]	1.2	1.4
Holland (n = 364)[8,111]	0.8	1.1
Austria (n = 50)[8,111]	2.0	2.0
Switzerland (n = 137)[8,111]	2.2	1.5
Czech Republic (n = 1,366)[23]	0.3	0.7
USA (n = 77,191)[28]	3.4	0.3

concentrations of calcium and phosphate. Pure brushite stones consist of well formed, very compact crystals (**66**) and are thereby different from carbonate apatite stones, which are microcrystalline to pseudomorphic in structure. This strong structure means that brushite stones are difficult to remove using lithotripsy. Mixed stones consisting of brushite and weddellite are common.

The significance of calcium in the occurrence of brushite in the urine is shown in the nomogram in **67**. Pure brushite stones can only occur at very high calcium concentrations and in urine with a pH of between 6.5 and 6.8. If the urine pH increases to above 6.8, brushite can be transformed into carbonate apatite.

66



66 Brushite crystals in urine sediment. Basalt column-like crystals in scanning electron microscope image.

Permanent supersaturation of the urine with calcium and phosphate ions results in a strong tendency for brushite stones to recur. Citrate excretion in the urine is commonly reduced when brushite stones are present. There are many causes of hypercalciuria, for example, primary hyperparathyroidism or hyperadrenocorticism. In humans, other causes have been described including hypercalcaemia, complete or incomplete distal renal tubular acidosis, or a nonspecific loss of renal calcium. Dietary factors can also affect the occurrence of brushite stones.

> Brushite stones grow unusually quickly, so that after an initial manifestation, recurrence can occur within a few weeks.

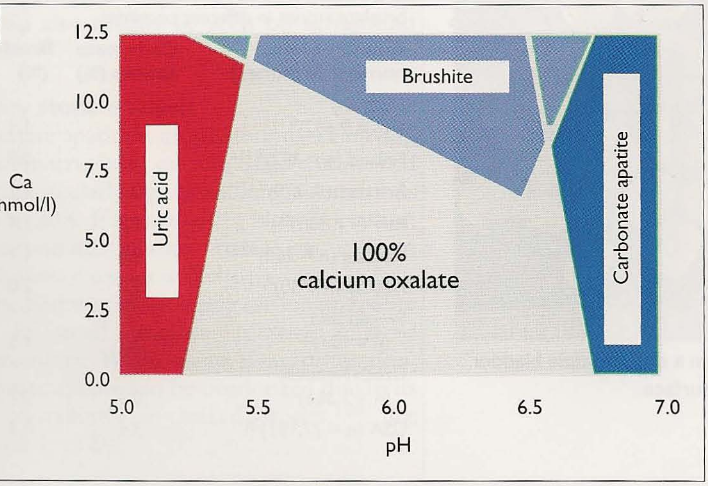
Brushite stones usually occur *independently* of infections. An accompanying urinary tract infection is usually secondary (**68**).

DIAGNOSIS

Urinalysis

- Specific gravity >1.030.
- pH 6.5–6.8.
- Characteristic, basalt column-like crystals in sediment (**29**).
- Quantitative urinary calcium assay – hypercalciuria.
- Quantitative urinary citrate assay – hypocitraturia.

67



67 Nomogram of the formation of different urinary stone phases as a function of the urinary pH and calcium concentration.[186]

Blood tests

Brushite stones do not lead to any haematological or biochemical changes unless the condition is bilateral in the kidneys or ureters with resulting renal failure.

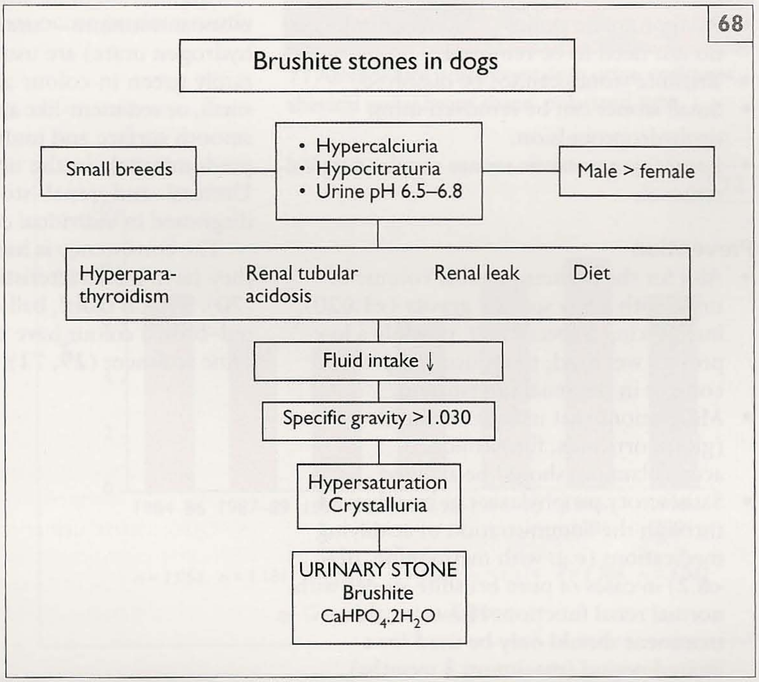
The total serum calcium, or ideally the ionized calcium, should be measured in dogs with pure brushite stones. In the presence of hypercalcaemia, serum PTH should be measured to exclude primary hyperparathyroidism.

Blood gas analysis is indicated if distal renal tubular acidosis is suspected.

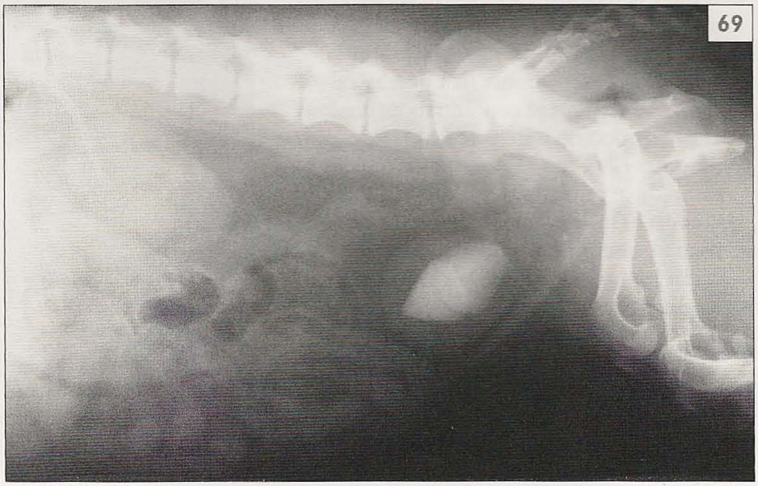
Diagnostic imaging

Brushite stones are radiopaque and can also be visualized with ultrasound (69).

68 Diagram of the pathogenesis of brushite stone formation.


68
Brushite stones in dogs
Small breeds
• Hypercalciuria
• Hypocitraturia
• Urine pH 6.5–6.8
Male > female
Hyperpara-thyroidism
Renal tubular acidosis
Renal leak
Diet
Fluid intake ↓
Specific gravity >1.030
Hypersaturation
Crystalluria
URINARY STONE
Brushite
$CaHPO_4.2H_2O$

69 Two large brushite stones in a 9-year-old female Dachshund with hypercalcaemia.



Urinary stone analysis

Even very small amounts of brushite in a urinary stone are an important indication of a high risk of recurrence. Weddellite appears frequently as a mixing partner. Most brushite stones are, however, monomineralic, which can indicate a potential calcium metabolism disorder and a high rate of recurrence. See Chapter 1.

TREATMENT AND PREVENTION

Treatment

- Asymptomatic stones (incidental findings) do not need to be removed.
- Brushite stones cannot be dissolved.
- Small stones can be removed using urohydropropulsion.
- Larger symptomatic stones require surgical removal.

Prevention

- Aim for the highest possible volume of urine with a low specific gravity (<1.020), introducing a special diet, possibly a low-protein wet food, to reduce the urea content in the renal interstitium.
- Medications that induce calciuresis (glucocorticoids, furosemide, acetazolamide) should be avoided.
- Satisfactory prophylaxis can be achieved through the administration of acidifying medications (e.g. with methionine, pH <6.2) in cases of pure brushite stones with normal renal function. However, this treatment should only be used for a limited period (maximum 3 months).
- If there is very low excretion of citrate in the urine, alkalinization is also recommended. However, a low urinary specific gravity is very important to ensure that urinary calcium and phosphate concentrations are low.
- If hypercalciuria is detected, thiazide diuretics (2–4 mg/kg orally, twice daily) can reduce calcium excretion via the kidneys. This treatment should not be used in cases of absorptive hypercalciuria as it can lead to soft tissue calcification.
- Regular (initially after 2–4 weeks) urinalysis (pH, sediment).
- Regular (every 3–6 months) radiography or ultrasound examination.
- Treat any identified primary cause (surgery for hyperparathyroidism[184], trilostane for hyperadrenocorticism[185]).

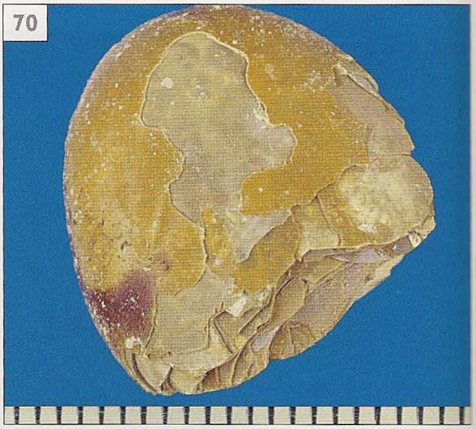
Ammonium urate stones

INTRODUCTION

Ammonium urate is a salt of uric acid. Uric acid is a weak acid that allows the formation of acidic and neutral salts through the systematic dissociation of two hydrogen ions. Urine generally provides the right conditions for the production of acidic salts, i.e. hydrogen ions are replaced by ammonium, sodium, or potassium ions.

Ammonium urate stones (more accurately: monoammonium urate or ammonium hydrogen urate) are usually yellow to brown, rarely green in colour and are almost always small, or sediment-like and round. They have a smooth surface and multiple stones are found predominantly in the urinary bladder (97%). Ureteral and renal stones have also been diagnosed in individual cases.

The consistency is hard, rarely porous, and they have a characteristic shell-like structure (70). Typical radial, ball-shaped crystals with a red–brown colour have been demonstrated in urine sediment (29, 71).

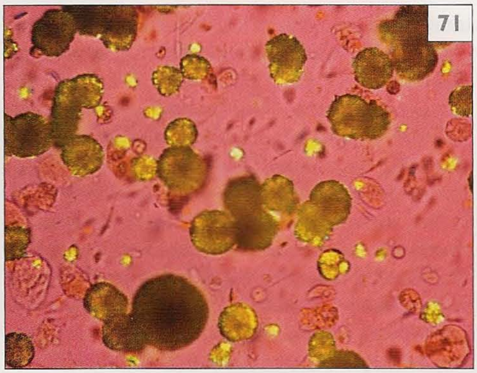


70 Ammonium urate stone from a dog.

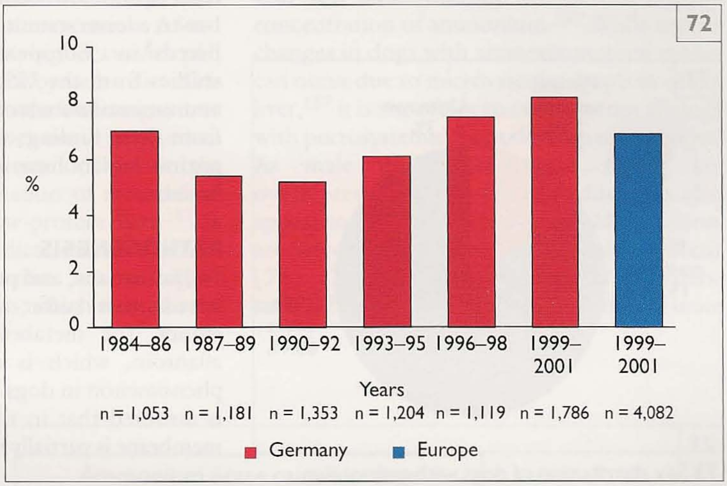
EPIDEMIOLOGY

The frequency of ammonium urate stones ranges between 5 and 11%.[23,24,24a,24b,29,33,34,64,187,188] In Europe, ammonium urate stones were 5.2–8.2% of stones found in dogs in 1984–2001 (72). The frequency of ammonium urate stones in dogs does not appear to have changed over time.

Fifty-five to 80% of ammonium urate stones are diagnosed in Dalmatians (*Table 30*). Furthermore, all studies have shown that ammonium urate stones occur predominantly



71 Ammonium urate crystals in urine sediment, sherical radial beam shape, polarized light.



72 Percentage frequency of ammonium urate stones in dogs from different periods of time in Germany and Europe (n = total number of stones).

Table 30 Breed distribution (%) in dogs with ammonium urate stones in different regions.[8,10,23,24,28]

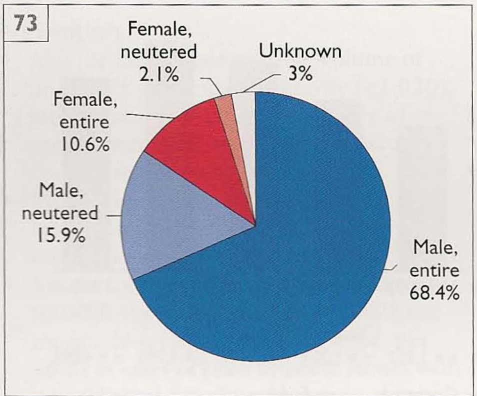
Breed	Europe	Germany	Czech Republic	Canada	USA
Total stones (n)	**4,082**	**7,697**	**1,366**	**16,000**	**77,191**
Ammonium urate (n)	**282**	**1,031**	**126**	**797**	**6,144**
Dalmatian	55.7	69.7	80.2	69.8	61
Yorkshire Terrier	9.9	8.8	8.7	2.8	5.0
Crossbreed	4.6	1.2	1.6	3.8	0
Shih Tzu	3.6	5.2	1.6	6.4	4.0
Dachshund	3.2	3.0	0	0	0
Cocker Spaniel	2.8	4.2	4	0	0
English Bulldog	2.8	0	0	3.8	4.0
Pekingese	1.1	2.7	1.6	0	0
Schnauzer	1.1	8.4	0.8	4.8	7.0
Jack Russell	1.1	0	0	0	0

in male dogs (80 to >90%). In a European study, 84% of the dogs affected were male (**73**).[1,23,24,24b,24c,34,64,187,188]

> Ammonium urate stones are typical urinary stones in Dalmatians.

From these observations, a sex-dependent alteration in purine metabolism was often proposed. However, many other studies have found this to be unlikely.[189] Other diseases that are typical of Dalmatians and are linked to purine metabolism, such as deafness and skin changes, appear in both sexes to an equal extent.[190] It is therefore now generally accepted that the predominance of stones in male dogs is related to anatomical differences. Ammonium urate stones are generally rounded and smooth, they are therefore often voided asymptomatically in the urine of female animals.

73



73 Sex distribution of dogs with ammonium urate stones, European study 1999–2001 (total number: n = 4,082, ammonium urate: n = 282).[8]

Dogs with ammonium urate stones are, on average, younger than dogs with struvite or calcium oxalate stones. In studies from the USA[187,188] the average age was 4.5 years, in the Czech Republic 5.2 years[23], and in Europe 6.3 years (**74**).

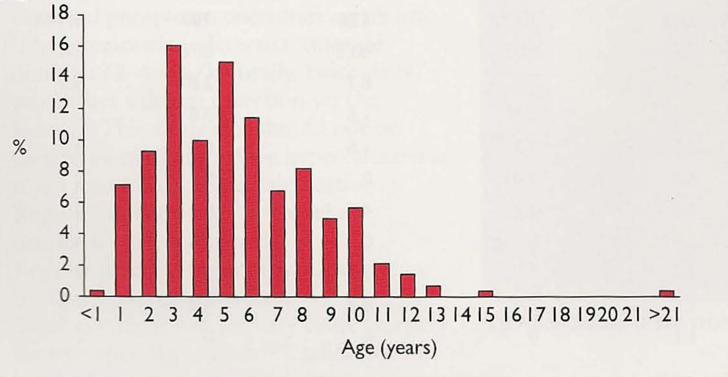
In a European study, 76% of the dogs with ammonium urate stones were *under* 7 years of age, while around 76% of the dogs with calcium oxalate stones were *over* 7 years old.[8]

Apart from Dalmatians (the predominant breed to suffer from ammonium urate stones), these stones also occur in many other breeds but to a lesser extent (*Table 30*). A total of 40 breeds[8] in a European study and 66 breeds in studies from the USA, were diagnosed with ammonium urate stones. It must be assumed from these findings that genetic disorders of purine metabolism can also occur in other breeds.

PATHOGENESIS

In Dalmatians, and presumably dogs of other breeds that suffer from ammonium urate stones, the metabolism of uric acid into allantoin, which is a normal physiological phenomenon in dogs (see **9**), is diminished. It is assumed that in these dogs, the liver cell membrane is partially impermeable to uric acid.

74



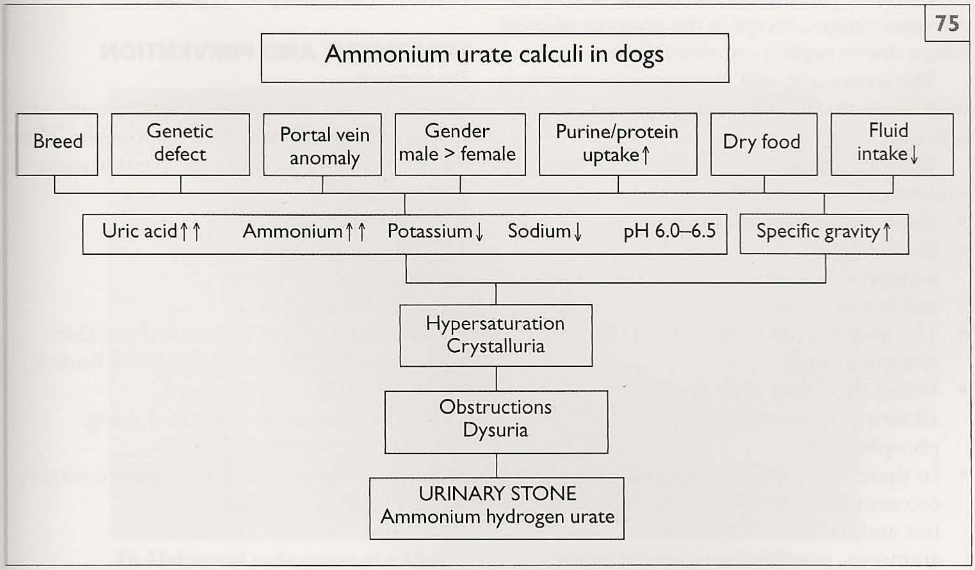
74 Age distribution of dogs with ammonium urate stones in Europe 1999–2001 (n = 282).[8]

Furthermore, in normal dogs, 98–100% of glomerular filtrated uric acid is reabsorbed into the proximal tubule system and further metabolized by the liver. In Dalmatians, this reabsorption is disrupted, which leads to increased uric acid excretion.[49] As this disorder is prevalent in Dalmatians, but not all Dalmatians produce urinary stones, other factors must contribute to the formation of ammonium urate stones.

The pH is an important factor for the crystallization of urates in urine. A urine pH of <5.7 leads to the crystallization of uric acid, while a urine pH of >6.3 crystallizes ammonium urate; between these values, a mixture of the two occurs.[191]

Diet has a strong influence on urine pH and on uric acid and ammonium excretion. A low-protein diet leads to a higher urine pH. Phosphate intake is reduced by such a diet. This can lead to an imbalance in the buffering system of urine and a compensatory rise in ammonium formation from glutamine. This is the hypothesis for the formation of ammonium urate stones even with low-protein diets.[187] In protein- and purine-rich diets, more uric acid is excreted and acidic urine has a higher ammonium concentration, which increases the risk of urate stones.[192] Potassium and sodium deficiency also leads to increased ammonium excretion.[193] It has also been proposed that reduced excretion of inhibitors in urine can promote the formation of ammonium urate stones.[194] For example, Dalmatians with urate stones excrete significantly less Tamm-Horsfall proteins than healthy Dalmatians.

A high incidence of urate stones has been found in dogs with portal anomalies.[195,196] This vascular anomaly leads to reduced liver circulation and thereby liver function, and results in a reduction in the conversion of uric acid into allantoin and of ammonia into urea. Dogs with a portosystemic shunt were found to have increased serum concentrations of uric acid and ammonia and an increased urine concentration of ammonium.[187] While similar changes in dogs with ammonium urate stones can occur due to microvascular dysplasia of the liver,[187] it is important to note that not all dogs with portosystemic shunt develop urate stones. As male dogs with urate stones are overrepresented, urinary flow disorders also appear to play an important role. Many factors are necessary for urate urolithiasis to occur (**75**). Other severe liver function disorders, such as hepatic cirrhosis, can also promote urate


75
Ammonium urate calculi in dogs
Breed
Genetic defect
Portal vein anomaly
Gender male > female
Purine/protein uptake↑
Dry food
Fluid intake↓
Uric acid↑↑
Ammonium↑↑
Potassium↓
Sodium↓
pH 6.0–6.5
Specific gravity↑
Hypersaturation
Crystalluria
Obstructions
Dysuria
URINARY STONE
Ammonium hydrogen urate

75 Diagram of the pathogenesis of ammonium urate stones in dogs.

stone formation. A high-grade low-protein diet[145] can also contribute. However, both problems only rarely cause urate urolithiasis.

DIAGNOSIS

Urinalysis

- Specific gravity: mostly >1.030, except in the presence of a portosystemic shunt, when it is mostly hyposthenuric (<1.008) or isosthenuric (1.008–1.012).
- pH: fasted, usually 6.0–6.5.
- A urate crystalluria (**29, 71**) is not proof of an ammonium urate stone, but should always be monitored carefully in all dogs, with the exception of Dalmatians, as there is an increased risk of stone formation. Crystalluria is not present in all dogs with urate stones. Dalmatian puppies often have urate crystalluria, which usually disappears once the animal reaches adulthood without the formation of urate stones.[187]
- Microbial monitoring (a secondary urinary tract infection can occur with ammonium urate stones).
- Where possible, a quantitative assay can be made of uric acid and ammonium in the urine.

Blood tests

In Dalmatians and other breeds with ammonium urate stones but without liver disease, all biochemical parameters are usually within the reference ranges, except in the presence of renal failure due to nephro- or ureteroliths.

The serum uric acid concentration increases with urate urolithiasis, independently of their aetiology.

The following findings are typical in dogs with a portosystemic shunt or microvascular dysplasia:

- Haematology reveals microcytosis.
- Biochemistry: reduced urea and hypoproteinaemia with hypoalbuminaemia and hypoglobulinaemia.
- The liver enzymes are often in the reference range.
- Young dogs may present with increased alkaline phosphatase, calcium, and phosphorous.
- In these dogs, hepatic function tests are recommended with a bile acid stimulation test and/or test for the presence of ammonia, possibly an ammonia tolerance test.

Diagnostic imaging

Urate and uric acid stones are difficult to see as they are weakly radiopaque to radiolucent (**76**). Ultrasonography is the most reliable way of visualizing these stones, but it is difficult to determine their size and number. Double-contrast cystography can be used instead of ultrasonography. This is minimally invasive, it is not necessary to sedate the animal, and all of the stones are shown.

In dogs with a congenital portosystemic shunt, the radiograph shows a small liver. A definitive diagnosis can be achieved with ultrasonography (Doppler), portography, splenoportography, or scintigraphy.

Urinary stone analysis

All urinary stones should be sent for analysis, even when there are several of them. The diagnosis can then be confirmed, as sodium and potassium urate, or uric acid can appear as pure stones. Where there is a urinary tract infection, struvite and carbonate apatite can be found as pure stones or as mixing partners with ammonium urate, even in Dalmatians.

Chemical urinary stone analysis using test kits cannot differentiate between the individual urates and have a higher rate of errors, they are therefore obsolete.[3,100,141]

Analysis using infrared spectrometry provides definitive qualitative and quantitative results.[100] See Chapter 1, p. 30.

TREATMENT AND PREVENTION

Treatment

Spontaneous dissolution of ammonium urate stones appears to be almost impossible. These cases therefore require a combination of treatments:[187]

- Low-purine diet.
- Xanthine oxidase inhibitor.
- Alkalinization of urine.
- Increased diuresis.
- Investigate causes and treat if possible.
- Asymptomatic stones (incidental finding) do not need to be removed.
- Small stones can be removed using urohydropropulsion.
- Large symptomatic stones require surgery for complete removal.

Diet

A diet with a low purine content is needed to dissolve and prevent ammonium urate stones. This can be achieved with a reduced protein content (10–18% of dry matter), but purine-rich ingredients (see Appendix, p. 147) should also be avoided and replaced with low-purine ingredients (eggs, dairy products, vegetable proteins). A low-protein diet reduces urea production, thereby decreasing the excretion of ammonium ions. The reduced protein content has the added effect of reducing the urea concentration in the interstitium of the renal medulla, thereby reducing the concentration gradient ('medullary wash-out') and resulting in the production of more urine with a lower specific gravity. Wet diets also increase urine production.

Commercial diets have been developed that influence the composition of urine very effectively for the dissolution and prevention of ammonium urate stones.

Severely protein-resticted diets should not be fed long-term to growing animals. The addition of low-purine protein such as casein to a very low-protein diet doubles the excretion of ammonium urate in the urine[197] and no longer produces the desired effect in urine.

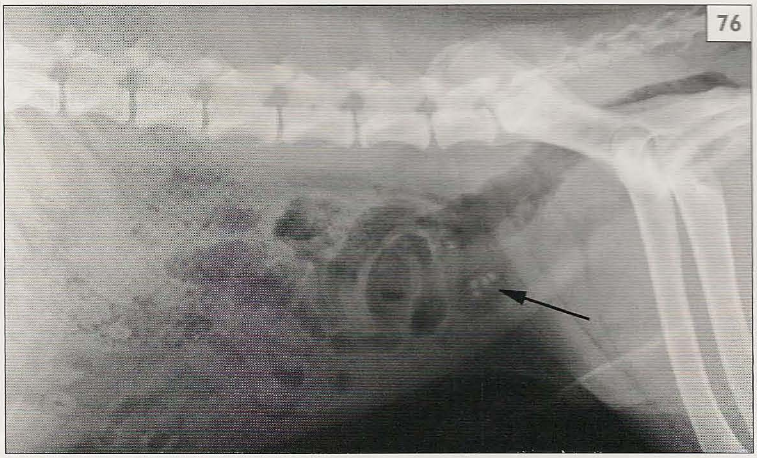
Alkalinization of the urine

Urate stones grow in acidic urine and can possibly be dissolved in alkaline urine. The aim is to achieve a urine pH of >7.0 but not >7.5, otherwise there is a risk of calcium phosphate stone formation. A low-protein diet does lead to alkalinization; however, additional alkalinization using sodium bicarbonate (25–50 mg/kg orally q12h) or potassium citrate (50–150 mg/kg orally q12h) could be necessary. The dosage must be adapted to the patient and the urine pH.

Pharmacological management

Allopurinol readily binds to xanthine oxidase and inhibits its effect. The production of uric acid is thereby reduced as hypoxanthine no longer changes to xanthine and xanthine no longer changes to uric acid (**9**). A side-effect is an increase in serum xanthine concentration, which is then excreted in the urine.

Allopurinol is administered at a dose of 10–15 mg/kg q12h orally to dissolve urate stones. Side-effects are rare, but in dogs the formation of xanthine stones can be a problem.[5,43,44] Sometimes a xanthine coating forms around existing urate stones. For this reason, allopurinol should only be used in



76 Abdominal radiograph of a 10-month-old Golden Retriever with urate stones in the bladder (arrow), caused by a portosystemic shunt.

conjunction with a low-purine diet. Side-effects such as haemolytic anaemia, gastrointestinal disorders, or exanthema, which are described in humans, rarely appear in dogs.[187] Since allopurinol is excreted by the kidneys, the dose should be reduced in patients with renal failure.

Allopurinol, in conjunction with the appropriate diet, produced complete dissolution of ammonium urate stones in 9/25 of dogs (36%), partial dissolution in 8/25 of dogs (32%), and had no effect in the remaining 8 dogs (32%).[187] The average length of time for stone dissolution was 3.5 months (range: 1–18 months).

Further measures

Some small symptomatic bladder stones can be removed using urohydropropulsion. Large bladder or kidney stones should be removed surgically if they are symptomatic. Bacteriology on urine obtained under sterile conditions should be performed regularly, as the presence of stones entails a higher risk of urinary tract infection, which may be associated with infection-induced struvite stones.

In dogs with a congenital portosystemic shunt and ammonium urate stones, the vascular anomaly should be corrected as early as possible after appropriate management (hepatic diet, lactulose, antibiotics). To eliminate the risk of recurrent stone formation and other clinical signs, minimally invasive occlusion with a coil,[198] or surgery is indicated. Symptomatic stones should be treated appropriately (allopurinol, diet, alkalinization of urine) or removed (urohydropropulsion, surgery). Ammonium urate stones caused by a shunt rarely disappear after the successful closure of the shunt.[187]

As with other urinary stones, the animal should be encouraged to drink plenty. However, excessive dietary sodium should be avoided. Regular monitoring during stone dissolution, using double contrast radiographs and/or ultrasonography, is recommended to monitor therapeutic success and adjust the treatment if necessary. This treatment should be continued for up to 1 month after successful stone dissolution (small stones and sediment are not easily identified).

Owner compliance during stone dissolution treatment can be monitored via urinalysis (pH >7, specific gravity <1.020) and blood tests (reduced urea) (*Table 31*). Urine sediment should be monitored for the elimination of urate crystals (**29**, **71**). The uric acid/creatinine ratio in the urine is not helpful in dogs either for for diagnostic or treatment

Table 31 Evaluation of findings in history, clinical investigations, blood and urinalysis before, during and after urate stone dissolution.

Finding	Before treatment	During treatment	During prophylaxis
Haematuria	- to +++	↓	-
Pollakiuria	+ to +++	initially ↑ later ↓	-
Polyuria	- to +	+ to +++	+ to +++
Serum urea	Variable	<3.5 mmol/l	<3.5 mmol/l
Urine specific gravity	Variable	±1.004 to ±1.015	±1.004 to ±1.015
Urine pH	<7.0	>7.0	> 7.0
Urate crystals	- to +++	-	-
Bacteria in the urine	- to +++	-	-
Urine culture	- to +++	-	-
Urate stones: size and number	Small to large, few to many	Reduction in size and number	-

monitoring purposes, as this does not correlate to the 24-hour uric acid excretion in urine. The same can be said for the xanthine/creatinine ratio in urine when monitoring during the administration of allopurinol.[187]

Prevention

Ammonium urate stones have a higher rate of recurrence in Dalmatians (up to 30% in 1 year) than in other breeds. The following measures should therefore be taken:

- Maintenance on a low-purine diet. There is a potential problem in Dalmatians and English Bulldogs, as low-purine diets may predispose them to dilated cardiomyopathy due to insufficient carnitine intake.[187,199]
- Allopurinol (10–20 mg/kg daily, orally). Higher doses and administration without purine restriction increases the risk of xanthine stone formation.
- Alkalinization of the urine to a pH of around 7.0.
- Maintenance of increased fluid intake to increase the volume of urine.
- Regular urine bacteriology to check for infection, especially if struvite was found as mixed partner.

Sodium urate, potassium urate, and uric acid stones

Urate stones are always due to hydrogen urate (see ammonium hydrogen urate); this means that one hydrogen ion of uric acid is replaced by on alkaline ion (sodium, potassium). Thus the exact chemical name is sodium hydrogen urate or potassium hydrogen urate.

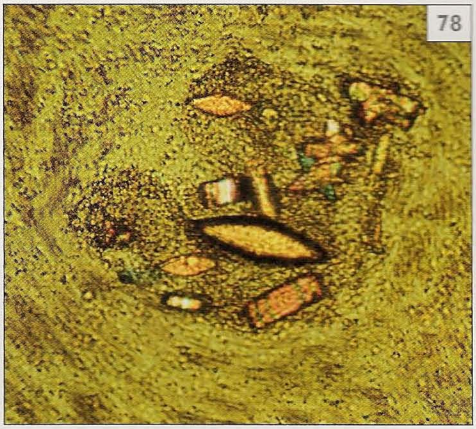
Sodium urate stones occur in 0.5–1% of cases, while potassium urate and uric acid stones are rarely seen (77). Interestingly, among 45 urinary stones analysed from Brazil, 7% were sodium urate and 2% were uric acid.[29]

Pathogenesis, diagnosis, and treatment for sodium and potassium urate stones are similar to those for ammonium urate stones.

In addition to high levels of uric acid in the urine, the formation of uric acid stones requires a urine pH <5.7 to allow crystallization to occur (**78**). Uric acid stones can be dissolved by simply increasing the alkalinity of urine to pH 6.5–7.0. The process can be accelerated with a low-protein diet and small doses of allopurinol (10–20 mg/kg/day).

Recurrence can be prevented by following the protocol given for ammonium urate stones.

77 Uric acid stones from a dog.



78 Uric acid dihydrate crystals in urinary sediment, whetstone-shaped and right-angled forms, polarized light.

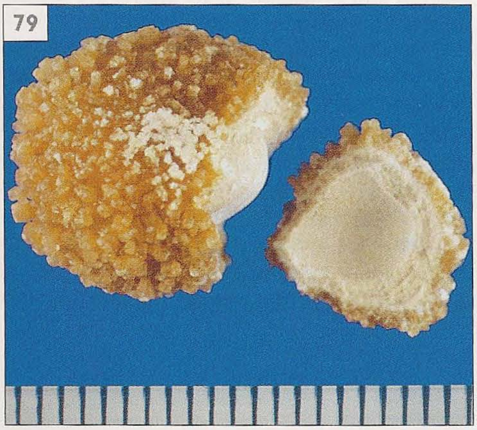
Cystine stones

INTRODUCTION

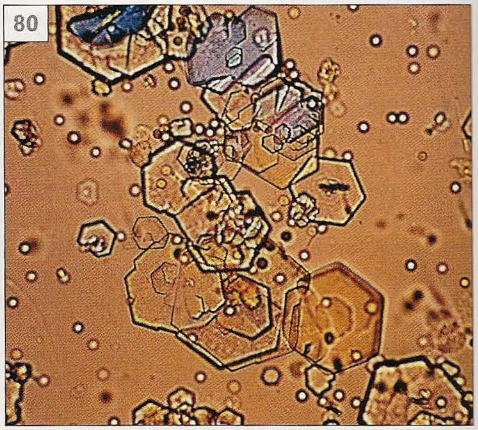
Cystine stones are honey yellow to red–brown in colour with a soft, fatty surface, which is rarely macrocrystalline (**79, 80**). However, the structure as a whole is solid. The connections between individual crystals are almost elastic, making lithotripsy using ultrasound or other percussion waves difficult. Cystine stones in dogs are generally spherical, and present as multiple small concretions, although they may occasionally present as larger, solitary stones.

EPIDEMIOLOGY

At the start of the 1980s, over 40% of stones analysed from dogs in Germany (n = 235) were composed of cystine.[200] Subsequently, the percentage of cystine stones in comparison with other types of stone went into a steady decline, dropping to 5–7% by 1999–2001 (**81**).[10,34,201,202] This reduction in cystine stones in Germany can probably be attributed to advances in the qualitative analysis of stones, and to the elimination of breeding with dogs genetically predisposed to stone development.

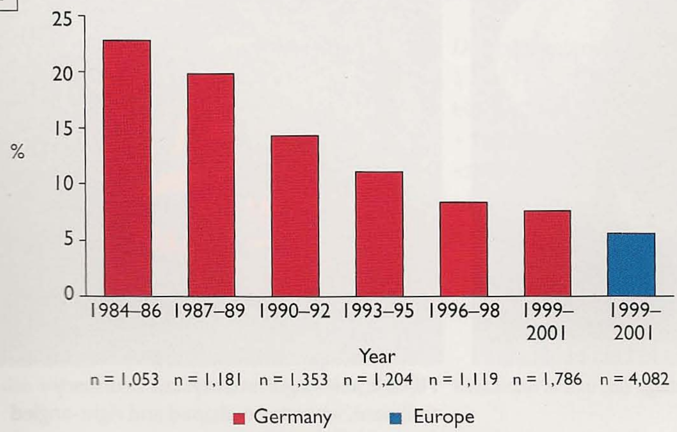


79 Cystine stone from a dog; pitted, microcrystalline surface.



80 Cystine crystals in urinary sediment, typical hexagonal shapes in polarized light.

81



81 Percentage frequency of cystine stones at various times in Germany, and in Europe in 1984–2001.[8]

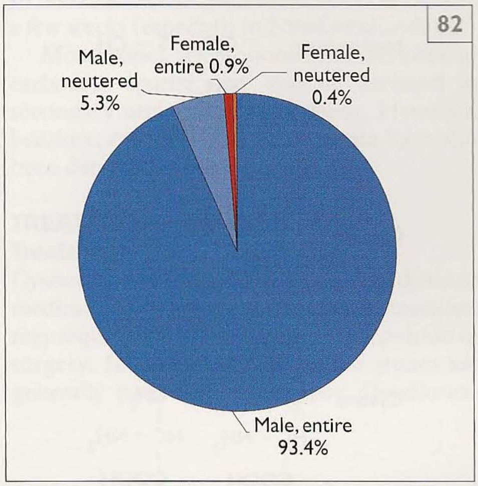
The frequency of cystine stones varies widely between countries (*Table 32*). There are marked differences within Europe, for example 0% in Norway and 11% in Poland; in North America, cystine stones are relatively rare, with a rate of 0.4–2.0%.

For a long time, cystine stones were only diagnosed in male dogs, so a sex-dependent inheritance was assumed.[204] However, in large studies, cystine stones were also found in bitches.[7,24] A European study (1981–2001) found a total of 1,031 cystine stones, 1% (n = 11) of which were from females.[10] 228 cystine stones were submitted in 1999–2001, three of which were from bitches (**82**).[8] The majority of cystine stones were diagnosed in intact dogs.

Due to the genetic predisposition, cystine stones occur in younger dogs than struvite or calcium oxalate stones (**83**). The average age is 4.8 ± 2.5 years (range: 1–14 years).[7]

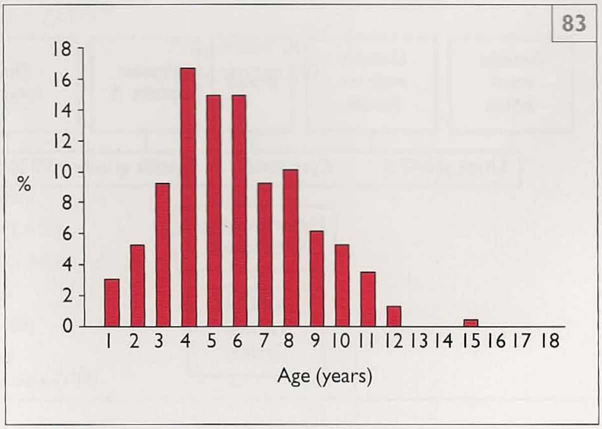
Table 32 Percentage frequency of cystine stones (1995–2005) in various countries (n = total number of urinary stones).[8]

Country	%
Poland (n = 56)[8,111]	10.7
Germany (n = 1,787)[8,111]	7.6
Italy (n = 429)[8,111]	6.5
Austria (n = 50)[8,111]	6.0
Czech Republic (n = 1,366)[23]	5.6
Switzerland (n = 137)[8,111]	5.1
France (n = 270)[8,111]	4.8
Spain (n = 77)[8,111]	3.9
Belgium (n = 91)[8,111]	2.2
Netherlands (n = 364)[8,111]	2.2
USA (n = 5,375)[203]	2.0
Finland (n = 392)[8,111]	1.8
Great Britain (n = 118)[8,111]	1.7
USA (n = 77,191)[28]	1.0
Mexico (n = 200)[24c]	0.5
Canada (n = 16,000)[24]	0.4
Brazil (n = 45)[29]	0.0
Norway (n = 93)[8,111]	0.0



82 Sex distribution of dogs with cystine stones, European study 1999–2001 (total stones: n = 4,082, cystine: n = 228).[8]

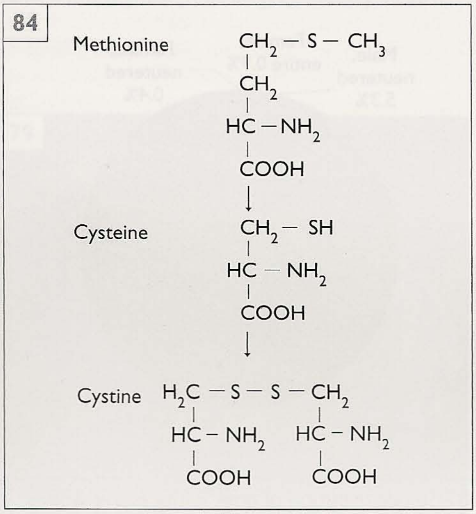
83 Age distribution of cystine stones in a European study 1999–2001 (n = 228).[8]



PATHOGENESIS

Cystine is formed metabolically from L-methionine via the precursor cysteine (**84**). Cysteine is highly soluble in urine, but is largely oxidized to cystine prior to renal excretion. This metabolic route can be partially reversed by reduction in the final stage (cysteine → cystine), since cystine can be converted back to the highly soluble cysteine in bladder urine by the administration of high doses of ascorbic acid.[141,205,206]

84

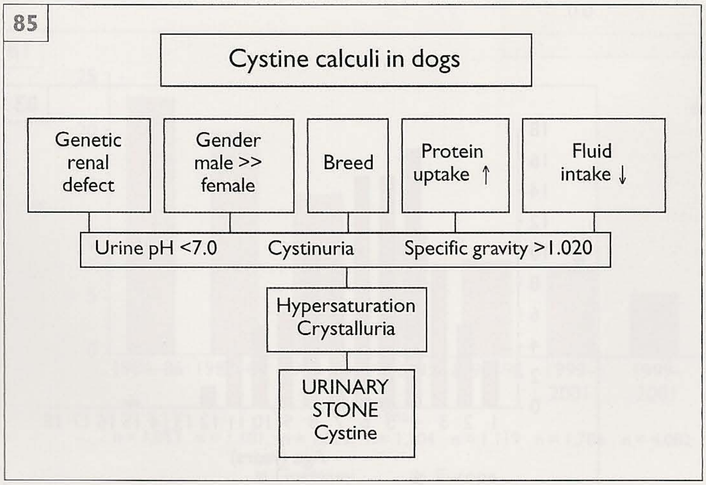

Methionine
CH_2-S-CH_3
CH_2
$HC-NH_2$
COOH
Cysteine
CH_2-SH
$HC-NH_2$
COOH
Cystine
$H_2C-S-S-CH_2$
$HC-NH_2$
$HC-NH_2$
COOH
COOH

84 Chemical structure of methionine, cysteine, and cystine.

Cystinuria is a genetically determined renal defect leading to the reduced reabsorption of particular amino acids, of which only cystine is poorly soluble in urine (for detailed description see Chapter 1) (**85**). This anomaly probably stems from an autosomal recessive inheritance, and is particularly prevalent in certain breeds of dog (*Table 33*).[37,207] A European study showed that cystine stones are most likely to occur in Irish Terriers, Bassets, and Munsterlanders, while, in Germany, Dachshunds are overrepresented due to their widespread popularity.[8,10] In North America, cystine stones are especially common in English Bulldogs (17–20%) and Newfoundlands (5–9%).[7,24] Cystine stones have been found in over 60 breeds so far.

The higher proportion of male dogs with cystine urolithiasis is now attributed to the anatomy of the lower urinary tract. Cystine stones are generally small, their waxy surface makes them slide easily, and they take a long time to develop into larger stones. They therefore pass through the short, wide urethra of females with ease, but can cause obstructions and retrograde flow in the long, anatomically constricted urethras of males.

85


Cystine calculi in dogs
Genetic renal defect
Gender male >> female
Breed
Protein uptake ↑
Fluid intake ↓
Urine pH <7.0
Cystinuria
Specific gravity >1.020
Hypersaturation Crystalluria
URINARY STONE Cystine

85 Diagram of the pathogenesis of cystine stone development in dogs.

DIAGNOSIS

Urinalysis

- Specific gravity: generally >1.035.
- pH: generally <6.8.
- Cystine urolithiasis can lead to bacterial urinary tract infections.
- Crystalline sediment: characteristic hexagonal crystals are a sure sign of cystinuria (but not of urolithiasis) (**29, 80**). Not all dogs with cystine stones have cystine crystals in the urine.
- Possible quantitative determination of cystine excretion in urine[208,209]
  - Normal: <660 µmol/l.
  - Metastable range: 660–1,200 µmol/l.
  - Pathological: >1,200 µmol/l.

Blood testing

There are no specific changes unless renal failure is present due to renal or urethral calculi.

Regular haematology is indicated during treatment with tiopronin as thrombocytopenia may develop.

In Newfoundlands[210] and Landseers, a polymerase chain reaction (PCR) analysis on a blood sample (EDTA) or cheek swab can reveal whether the animal has the genetic defect.

Diagnostic imaging

Cystine stones are weakly radiopaque. It is therefore easy to overlook small stones. Cystine stones are easily indentified with ultrasonography, but it is difficult to determine the size and number of stones with this method. Double-contrast cystography can be used to identify and count even small stones. (see *Table 14*, p. 45).

Urinary stone analysis

Urinary stone analysis provides a diagnosis of the genetic defect for cystinuria. See Chapter 1. In 50–75% of cases, the condition recurs within a few weeks (especially in Newfoundlands).[211]

Most stones are monomineral. Struvite or carbonate apatite may also be detected in secondary urinary tract infections. However, brushite, calcium oxalate, and urate have also been detected in cystine stones.

TREATMENT AND PREVENTION

Treatment

Cystine stones can be dissolved using diet and medication. Symptomatic stones (obstruction) may require removal by urohydropropulsion or surgery. In bitches, small cystine stones are generally passed spontaneously. Dissolution

Table 33 Dog breeds showing a predisposition for the development of cystine stones, Germany 1984–2001 (n = 7,697).[10]

Breed (total stones)	**Proportion of cystine stones (%)**
Irish Terrier (55)	81.8
Basset (82)	63.4
Munsterlander (58)	51.7
Rottweiler (88)	38.6
Dachshund (1,418)	31.2
Crossbreed (1,365)	13.2
Poodle (406)	7.6
Bull Terrier (68)	7.4
Standard and Giant Schnauzers (107)	2.1

treatment should be continued until 1 month after the complete radiological or ultrasonic disappearance of the stones.

Treatment to dissolve stones includes the following measures:

- Reduction of methionine in the diet.
- Increased diuresis.
- Alkalinization of urine to increase solubility of cystine.
- Medication to promote the formation of easily soluble disulphide.
- Reduction of cystine to cysteine.
- Regular monitoring during dissolution treatment (urinary pH, specific gravity, sediment; radiographs) (*Table 34*).

Reduction of methionine in the diet

All foods containing animal protein contain large quantities of methionine (see Appendix, p. 151), which is mostly metabolized to cystine. Other foods, such as eggs, wheat or peanuts are also rich in methionine. It therefore makes sense to reduce protein intake to the required level only. Dietary modification alone will not result in dissolution and should be accompanied by other measures.[32]

A low-protein, low-sodium, alkalinizing diet could reduce the proportion of cystine in the urine of dogs with cystine stones by 20–25% compared to normal tinned dog food.[211] It is important that no other type of food be given in addition to the low-protein food. Owner compliance can be checked relatively simply by measuring serum urea concentration (*Table 34*).

In humans, studies have shown that excessive salt intake leads to increased urinary cystine excretion.[212] Reduction of sodium in the diet is therefore recommended. Similar studies have yet to be performed in dogs.

The degree of protein reduction has not been clearly established, especially since dogs with cystinuria often also excrete more carnitine in their urine. A low-protein diet may thus lead to carnitine deficiency, which can result in the development of dilated cardiomyopathy.[213] Carnitine (50–100 mg/kg orally q8h) and taurine (500 mg orally q12h) supplementation is therefore recommended for animals with cystinuria on low-protein diets.[39]

Low-protein, alkalinizing, low-sodium commercial pet foods have been developed, which can be very effective in the treatment and prevention of cystine stones.

Increased diuresis

The supersaturation of urine with cystine is proportional to the cystine concentration, since no inhibitors of cystine crystallization have yet been found in urine. Therefore, the reduction of urine specific gravity throughout the day is both the most important and simplest method of reducing cystine saturation. In humans, cystine excretion follows a circadian rhythm, with the highest concentrations occurring at night;[214] it is not clear if this is also true in dogs. Wet food is recommended.

The low protein content of a cystine stone dissolving diet has the beneficial side-effect of medullary wash out (less urea available to sustain a concentration gradient in the interstitium, leading to less concentrated urine).

Specific gravity should be maintained at <1.020 during the dissolution of stones, and during prophylaxis.

Alkalinization of urine with resultant increase in cystine solubility

Cystine is poorly soluble in urine of normal pH (5.5–7.0); its solubility steadily increases above a pH of 7.5 (**86**). This is the basic principle behind the treatment to dissolve and prevent cystine stones. Improving the solubility of cystine through the alkalinization of urine is an established and successful treatment in human medicine.[97,215] Potassium citrate is preferable to sodium bicarbonate, because there is some evidence that sodium stimulates cystine excretion.[212,215] Alkalinization is particularly important overnight, since this is when the urine pH is at its lowest.[177]

There are no scientific studies into the successful application of alkalinization treatment in dogs,[7,32,216] but the administration of potassium citrate does increase canine urinary pH[177] and thus improves cystine solubility (**86**). In humans, sodium citrate should not be given after the administration of salt because of possible increased cystine excretion.[212] This remains unclear for dogs.

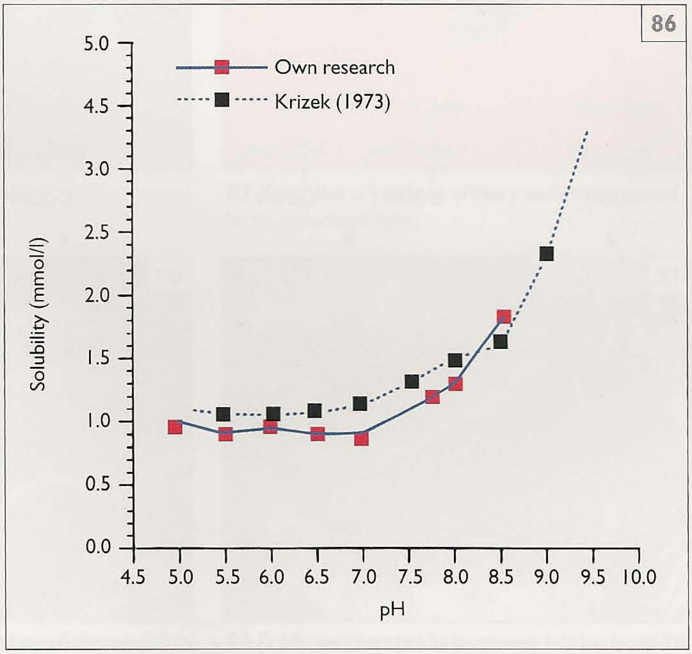
Potassium citrate can be mixed into food. Urine pH should be checked regularly to adjust the dose, with the target pH ≥7.5. It should be remembered that calcium phosphate stones can also develop at this urine pH level.

Medication to form highly soluble disulphide

A further treatment principle acts on the metabolism, before cysteine is oxidized to cystine, since other compounds with terminal

Table 34 Evaluation of results in history, clinical examination, blood and urinalysis prior to and during dissolution of cystine stones.[211]

Result	**Prior to treatment**	**During treatment**	**During prophylaxis**
Haematuria	- to +++	↓	-
Pollakiuria	+ to +++	Initially ↑ later ↓	-
Polyuria	- to +	+ to +++	+ to +++
Serum urea	Variable	<3.5 mmol/l	≤3.5 mmol/l
Urine specific gravity	Variable	±1.004 to ±1.014	±1.004 to ±1.014
Urine pH	<7.0	>7.0	>7.0
Inflammation in urine	- to +++	↓	-
Cystine crystals	- to +++	-	Variable
Bacteria in urine	- to +++	-	-
Urine culture	- to +++	-	-
Cystine stones: size and number	Variable, small to large	↓	-



86 Cystine solubility as a function of urinary pH.[1,109]

SH groups can react with cysteine to form a mixed disulphide. Tiopronin (2-mercaptopropionylglycine) or D-penicillamine can be used for this reaction. The resulting compound is highly soluble in urine (**87**).

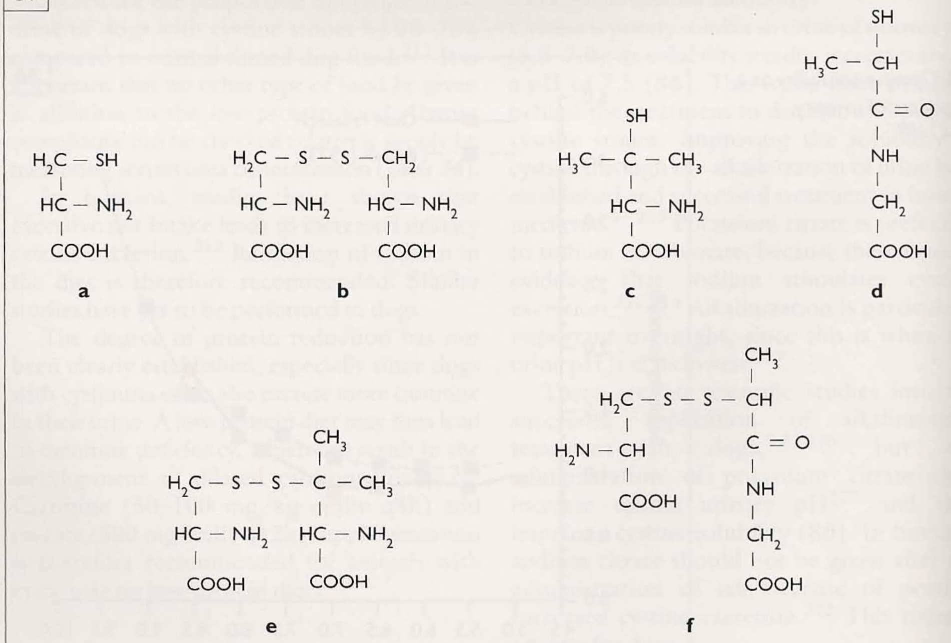
D-penicillamine, tiopronin, and captopril all contain SH groups, which can combine with cysteine to form a highly soluble disulphide; the latter, however, is not used for the treatment of cystine stones in veterinary medicine.[207,215,217-220]

- Tiopronin is associated with the fewest side-effects and is the most effective treatment for the dissolution of stones and also for the prevention of recurrence in dogs.[207] To dissolve stones, 30–40 mg/kg are given orally, divided into two doses. Stones were successfully dissolved in 9 out of 17 dogs, and the process took 2–4 months.[31,207] Side-effects include thrombocytopenia, anaemia, and raised liver enzyme levels.[211] Hypersensitivity reactions have been described and may also appear in dogs that are allergic to D-penicillamine.
- D-penicillamine, generally recognized as the first agent for the formation of mixed disulphide with cysteine, produces a 50-fold improvement in cystine solubility at alkaline pH.[221] The dose for dogs is 30 mg/kg orally divided into two doses. Gastrointestinal problems can occur at higher doses. Other common side-effects include pyrexia, hypersensitivity, and enlarged lymph nodes, which is why tiopronin is preferred.

Reduction of cystine to cysteine

Where urine cystine concentration is relatively low within the metastable range (660–1200 µmol/l), the reduction of cystine to cysteine by the administration of ascorbic acid has proved useful in human medicine.[3,97,101] It should be remembered that ascorbic acid is a weak acid, and thus slightly acidifies the urine. It is therefore essential to use an alkalinization treatment at the same time. Furthermore, ascorbic acid is partly metabolized to oxalate, which can lead to increased oxalate excretion in urine.

87



87 Biochemical structure of (**a**) cysteine, (**b**) cystine, (**c**) D-penicillamine, (**d**) 2-mercaptopropionylglycine, (**e**) cysteine-penicillamine disulphide, and (**f**) cysteine-2-mercaptopropionylglycine disulphide.

Prevention

Not all dogs with cystinuria will develop cystine stones. However, prophylaxis is recommended in such dogs, as well as in those where cystine stones have been successfully dissolved or removed. Prophylaxis must continue throughout life. The measures already described for dissolving stones should therefore be continued:

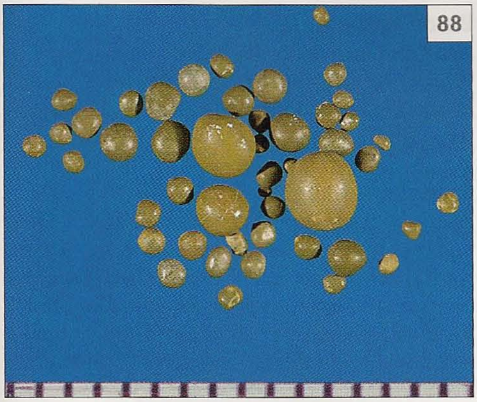
- Low-protein diet.
- Alkalinization of urine where diet alone is insufficient (target: pH >7.5).
- Tiopronin (15 mg/kg orally q12h). It is often possible to reduce or even discontinue tiopronin as the dog grows older.[216]
- Regular checks (pH, specific gravity, sediment) plus radiography or ultrasonography if required.
- Bacteriological urinalysis in cases when struvite was found as mixed partner.

> Dogs of any breed that manifest cystinuria with stone development should be excluded from breeding programmes. A PCR test is available to detect the genetic defect in Newfoundlands and Landseers.

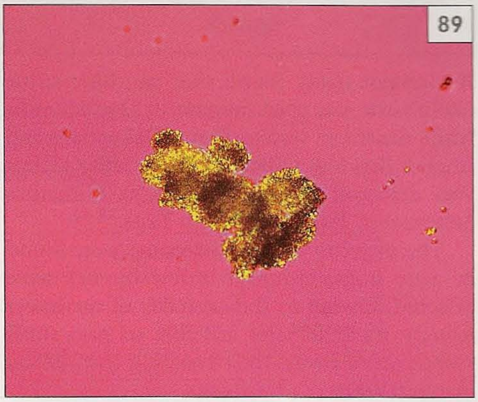
Xanthine stones

INTRODUCTION

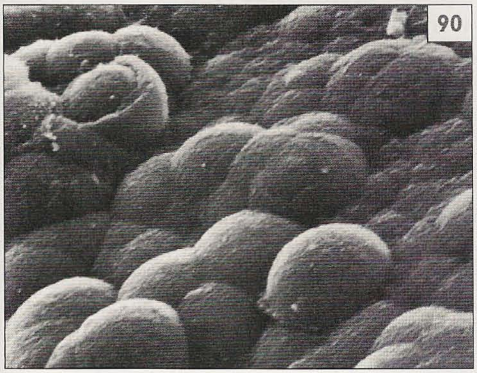
Xanthine stones appear as small round stones with a smooth surface (**88, 89**). Grit-like particless are also found. The stones are grey–brown to yellow, although green stones have been observed. The stones are generally built up in layers. The number of stones is usually very high (up to >100). Scanning electron microscopy shows a rounded surface with a fan-shaped internal structure (**90, 91**).[33,106]



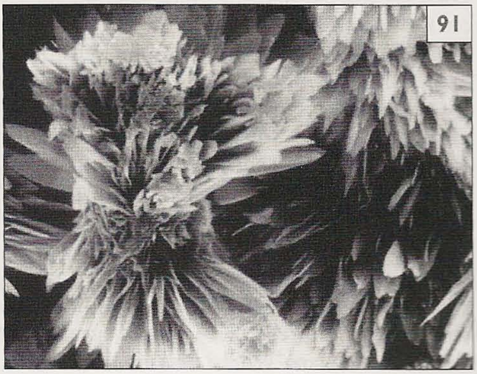
88 Xanthine stones from a dog.



89 Xanthine crystals in urinary sediment, round form, polarized light.



90 Scanning electron microscopy of the surface of a xanthine stone with a rounded shape.



91 Scanning electron microscopy of the fan-like internal structure of a xanthine stone.

EPIDEMIOLOGY

Xanthine stones are rare. They were first recorded in dogs in 1956.[222] The report describes three xanthine stones in a study of 26 dogs. This suggests that inadequate analytical methods may have produced a false result.[5] Three xanthine stones were discovered in an analysis of 741 urinary stones from dogs in Germany in 1986.[33] Of the stones investigated in the author's laboratory between 1984 and 2001 (n = 7,697), 22 were xanthine stones (0.3%).[10] Another large study from Canada (n = 16,000) found nine xanthine stones (0.05%); another from the USA (n = 77,191) found 50 (0.06%).[7,24,64,65] Interestingly, in Portugal 1.3% of 299 canine urinary stones were xanthine stones.[24b] Specific cases of xanthine stones have been described in particular breeds, e.g. Cavalier King Charles Spaniels or Dachshunds.[42,43,223]

> Xanthinuria is an autosomal recessive inherited disorder in Cavalier King Charles Spaniels.

A German study found that xanthine stone urolithiasis was predominant in Dachshunds, while American studies found Dalmatians and English Bulldogs to be particularly affected, but also detected xanthine stones in Miniature Schnauzers, Poodles, and Shi Tzus.[28,64]

The majority of xanthine stones were found in male dogs, although a few bitches were affected. Owing to the anatomy of the lower urinary tract, females are able to pass small stones more easily, thus avoiding the clinical manifestations of urolithiasis.

PATHOGENESIS

There are two pathways by which xanthine stones can form, both of which are dependent on purine metabolism (**9**). The first is caused by primary (congenital) xanthine oxidase deficiency, while the other arises from the secondary inhibition of xanthine oxidase following treatment with allopurinol (**92**). The consequence, in both cases, is xanthinuria. Most dogs with xanthine stones have a previous history of ammonium urate stones, and one study shows 35% of xanthine stones in dogs to be recurrent.[45]

Dogs with hereditary xanthine urolithiasis are very young, often less than 1 year of age and no older than 3 years. Where xanthine stones are secondary to allopurinol treatment (treatment for ammonium urate urolithiasis or leishmaniasis (Prof. A. Moritz, Giessen, personal communication), the dogs are often markedly older (4.8 ± 2.3 years).[28] Hereditary urolithiasis is thus highly probable in very young dogs (<12 months) with xanthine stones.

DIAGNOSIS

Urinalysis

- Specific gravity: generally >1.030.
- pH: generally <6.8.
- No changes detected with urine dipsticks.
- Rarely secondary bacterial urinary tract infection.
- Crystalline sediment – characteristic round, yellow–brown crystals (**29, 89**); often cannot be distinguished from ammonium urate crystals.
- High levels of hypoxanthine and xanthine excreted in urine.
- Low excretion of uric acid in urine.

Blood testing

Xanthine stones do not induce any changes in blood results, except where they occur bilaterally in the kidneys or ureters, leading to renal failure.

Diagnostic imaging

Xanthine stones are often very numerous. Their radiopacity is similar to that of urate stones; they are therefore easily overlooked. Double-contrast radiography is the method of choice for small stones, but they can usually also be visualized using ultrasonography.

Urinary stone analysis

Xanthine stones are generally associated with a high rate of recurrence (>50%). Urinary stone analysis provides a definitive diagnosis. Xanthine stones are generally monomineral, and very seldom contain impurities. The presence of ammonium urate and calcium oxalate has only been found where xanthine stones occur secondarily.[45] Following the administration of allopurinol in association with a nonpurine-reduced food, existing stones may develop a xanthine shell.

Xanthine cannot be detected using chemical urinary stone analysis with test kits, rendering this type of analysis obsolete.[100] Infrared spectrometry produces more reliable qualitative results. See Chapter 1, p. 30.

TREATMENT AND PREVENTION

Treatment

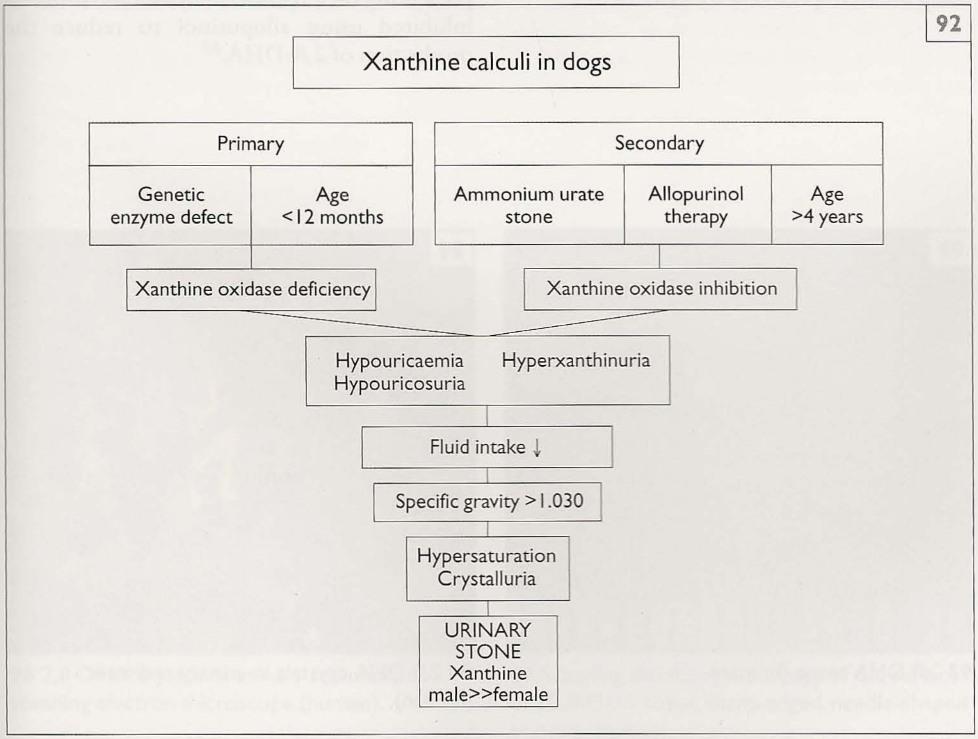
Since it is not possible to dissolve these stones, physical removal is the only remaining treatment option for symptomatic stones: urohydropropulsion for small stones, or surgery for large ones.

Prevention

To avoid the formation of xanthine stones (especially to prevent recurrence) the following measures are important (see also prevention of ammonium urate stones):

- Low-purine diet (see Appendix, p.147).
- Lowering the specific gravity of urine to <1.020.
- Where required, slight alkalinization of urine to pH 6.5–7.0.
- For secondary stone development, reduce the dose of allopurinol.

Animals with hereditary xanthinuria should be excluded from breeding programmes.


Xanthine calculi in dogs
Primary
Secondary
Genetic enzyme defect
Age <12 months
Ammonium urate stone
Allopurinol therapy
Age >4 years
Xanthine oxidase deficiency
Xanthine oxidase inhibition
Hypouricaemia Hypouricosuria
Hyperxanthinuria
Fluid intake ↓
Specific gravity >1.030
Hypersaturation Crystalluria
URINARY STONE Xanthine male>>female

92 Diagram showing the pathogenesis of xanthine stone development in dogs.

2,8-dihydroxyadenine stones

INTRODUCTION

2,8-dihydroxyadenine stones (2,8-DHA) stones (**93, 94**) are extremely rare in veterinary medicine. Crystalline deposits were found in the liver, kidney, and lymph nodes of 20 slaughtered cattle, which were clearly identified as 2,8-DHA using recognized methods of analysis (x-ray diffraction and infrared spectrometry).[224] One animal had deposits of 1–4 mm large, greenish urinary stones in the renal calices. The cause of the disease in cattle could not be established due to lack of data and blood samples, but a recently reported case of this kind of stone in a dog[88] suggests that it is worth giving a brief description of this rare type of stone. The report describes a 4-year-old, neutered male Schipperke of normal body weight. No crystals were found in the urinary sediment; urine pH was 6.5; specific gravity was 1.017. The stone was dark green with a rough surface (Dr. A. Moore, Guelph, personal communication). The diagnosis of 2,8-DHA stone was confirmed using infrared spectrometry (**95**).

PATHOGENESIS AND DIAGNOSIS

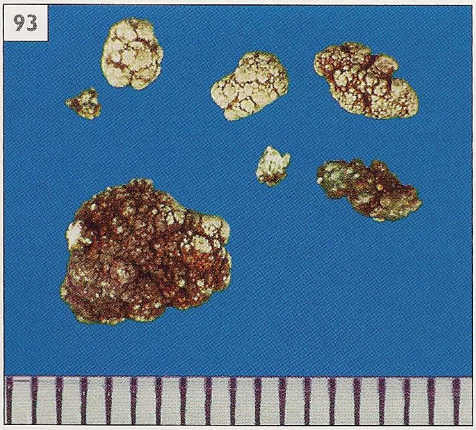
A genetic defect reduces the formation of adenine phosphoribosyltransferase (APRT), which is required for the metabolism of adenine into adenine monophosphate. If the genetic defect is only partial, the consequence in humans is an atypical gout.[225] In full APRT deficiency, adenine is oxidized to 2,8-DHA by xanthine oxidase via 8-hydroxyadenine. 2,8-DHA is poorly soluble in urine. In the absence of this genetic defect, this metabolic pathway does not occur and no 2,8-DHA will be detected in the urine.[55]

Detection of 2,8-DHA crystals in urinary sediment (**96**) is thus pathognomic for APRT deficiency, and provides an early indication of the composition of any stones present (**97**).

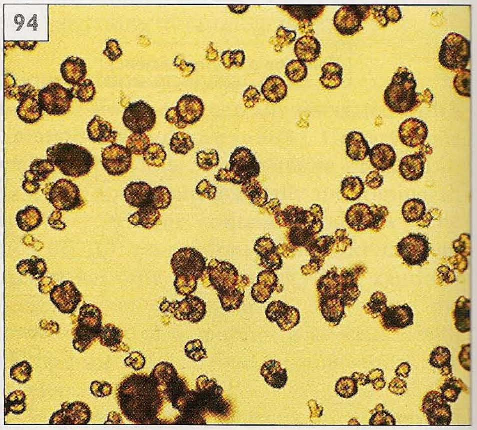
Because they are radiolucent, these stones in humans were initially confused with uric acid stones.[226] 2,8-DHA stones can be detected using ultrasound.

TREATMENT AND PREVENTION

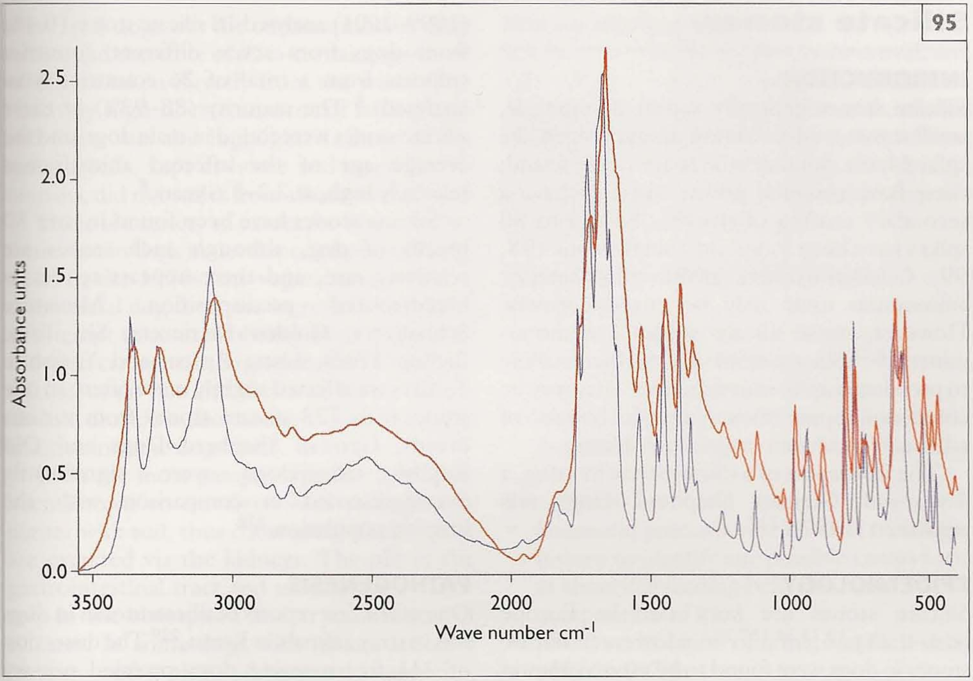
2,8-DHA stones cannot be dissolved, however, a highly effective treatment exists for preventing their recurrence: xanthine oxidase is inhibited using allopurinol to reduce the production of 2,8-DHA.[55]



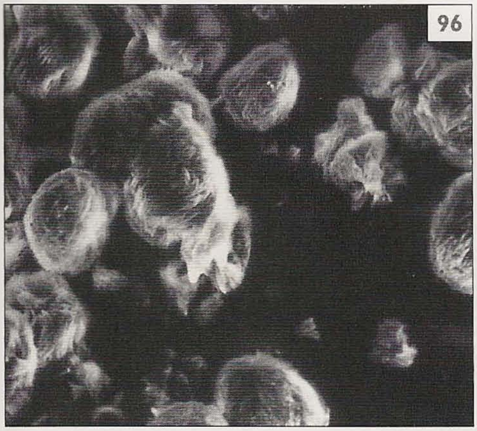
93 2,8-DHA stone (human).



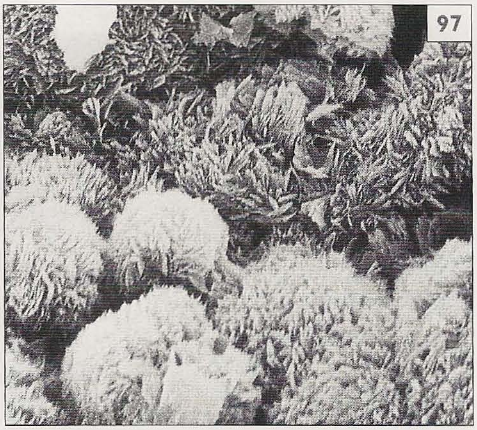
94 2,8-DHA crystals in urinary sediment (human).



95 FTIR spectrum of 2,8-DHA urinary stone (red) and reference substance (blue). (Picture by Dr A. Moore, Guelph, Canada.)



96 2,8-DHA crystals in urinary sediment, scanning electron microscope (human).



97 Scanning electron microscopy of the surface of a 2,8-DHA stone, sharp-edged, needle-shaped crystals (human).

Silicate stones

INTRODUCTION

Silicate stones generally appear as multiple, small stones, and are almost always shaped like spiked balls. Solitary stones are rarely found; these have rounded points and may have a secondary coating of struvite. Fifteen to 30 spikes have been found on a single stone (**98, 99**). Calcium oxalate, calcium phosphate, or ammonium urate may be mixed partners. However, most silicate stones are monomineral.[8,28] Silicate stones are microcrystalline to pseudoamorphous in structure. They may be composed of pure silicium dioxide, but also of salts such as calcium magnesium silicate.

The first report of a silicate stone in a dog, a 4-year-old German Shepherd Dog, was published in 1976.[227]

EPIDEMIOLOGY

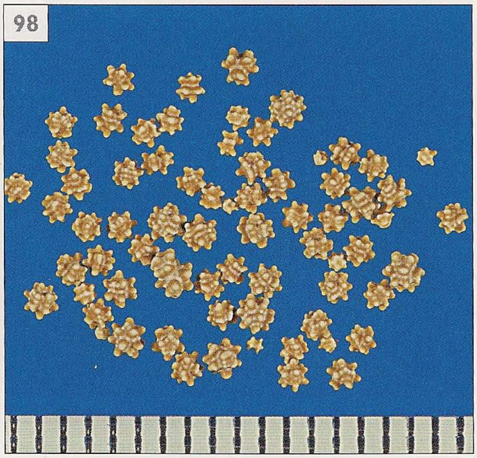
Silicate stones are very rare in Europe (0.1–0.2%).[10,23,34,107,202] However, silicate stones in dogs were found to be more common in the USA and Canada (0.2–1.8%) in investigations with large numbers of urinary stones.[24,28,228] Studies from Brasil (n = 45) and Mexico (n = 200) found silicate stones in 2% and 4%, respectively.[24c,29] One European study (1999–2001) analysed 18 silicate stones (0.4%) from dogs from seven different countries (reports from a total of 26 countries were analysed).[8] The majority (88–93%) of these silicate stones were found in male dogs, and the average age of the affected animals was relatively high, at 7.2–8.6 years.[8]

Silicate stones have been found in over 80 breeds of dog, although such stones are relatively rare, and there appears to be no breed-related predisposition. Miniature Schnauzers, Golden Retrievers, Shi Tzus, Bichon Frisés, Lhasa Apsos, and Yorkshire Terriers are affected slightly more often. In one study, with 773 silicate stones from various breeds, German Shepherd Dogs and Old English Sheepdogs were significantly overrepresented in comparison with the hospital population.[228]

PATHOGENESIS

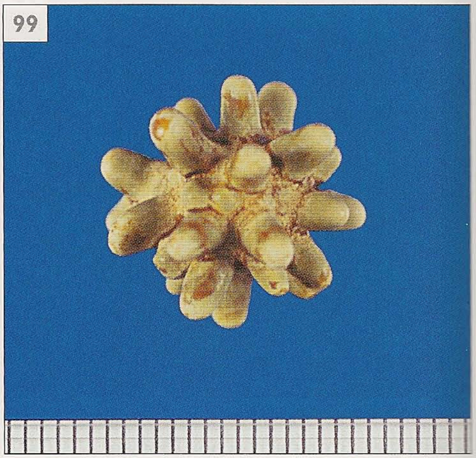
One of the first reports of silicate stones in dogs was in stray animals in Kenya.[229] The dissection of 241 free-roaming dogs revealed urinary stones in 53% of cases, nearly all of which were situated in the kidneys. Over 99% of the stones were composed of magnesium calcium aluminium silicate. The suggested possible cause for the development of silicate stones in

98



98 Multiple, spiky, rounded silicate stones from a dog.

99



99 Lone silicate stone.

these feral dogs was the consumption of dirty refuse, and therefore of silica-containing soil, or of silicate taken directly from the waste. The relatively high silicate content of local plants and water was also highlighted. Dogs of the same breeds, kept at home and cared for by humans, did not suffer from silicate urolithiasis.

There is a variety of causes for silicate stone formation in dogs in developed countries in the west. In the 1970s, the vegetable content of commercial dog food was increased – partly in an attempt to control obesity. Root vegetables and bran can contain large quantities of soluble silicate, as do rice and soy bean husks.[45] Fine silicium dioxide is also used as an anti-clumping additive in some dog foods.

Even the most pampered family pets have been known to eat dirty food or vegetable matter with soil, thus consuming silicates that are excreted via the kidneys. The pH in the gastrointestinal tract and urine plays a major role in the absorption and crystallization of silicates. In some dogs with silicate stones a history of pica (abnormal appetite, consumption of urine, earth, stones) or coprophagy was reported.[45] In experimental studies on dogs, silicate stones were also diagnosed after feeding silicates for several months.[230]

Silicate stones in humans have been found in several cases after the long-term administration of antacids (magnesium silicate or magnesium aluminium silicate).[231,232]

DIAGNOSIS

Urinalysis

- Specific gravity: >1.030.
- No characteristic crystals in sediment.
- Possible secondary infection.

Blood testing

Blood tests are unremarkable unless there is renal failure following bilateral nephrolithiasis.

Imaging

Silicate stones are faintly radiopaque in comparison with struvite stones. Silicate stones can be easily visualized using ultrasonography or double-contrast radiography.

Urinary stone analysis

Silicate stones are generally monomineral, and very rarely contain impurities. Definitive analytical results are only possible with infrared spectrometry, owing to their microcrystalline, pseudoamorphous structure. Struvite, ammonium urate, and calcium oxalate may also be present. See Chapter 1, p. 30.

TREATMENT AND PREVENTION

Treatment

- Silicate stones cannot be dissolved.
- Small stones may be removed using urohydropropulsion, and larger or multiple symptomatic stones require full surgical removal.

Prevention

- Successful prevention relies on a thorough history to identify any possible causes such as abnormal feeding behaviour and composition of food.
- Avoid acidification of urine; aim for a urine pH of 6.0–7.0.
- Urine dilution with a plentiful supply of fluids and a suitable diet; urine specific gravity <1.020.
- Ultrasound monitoring is recommended at regular intervals following successful removal of stones.

Drug-induced urinary stones

When considering the impact of drugs on urinary stone formation, it is important to distinguish between drugs that promote the development of what might be called classic urolithiasis, or whether the drugs themselves (or their metabolites) appear as urinary stones due to their solubility in urine.

Examples of classic stone development that can be amplified by drugs:

- Acidification treatment: uric acid, calcium oxalate, and cystine stones.
- Alkalinization treatment: phosphate stones.
- Ascorbic acid: hyperoxaluria – calcium oxalate stones.
- Corticosteroids, furosemide, acidification treatment, sodium chloride: hypercalciuria – calcium oxalate and/or calcium phosphate stones.
- Allopurinol: xanthine stones.

Drugs as urinary stones:

- First-generation sulphonamides may be poorly soluble in urine.
- Sulfadiazine (**100, 101**) and its metabolite acetylsulfadiazine.
- Tetracycline, trimethoprim.
- Fluoroquinolones: enrofloxacin.
- Antacids and their metabolites.
- First-generation HIV-drugs (indinavir) (human medicine).

PATHOGENESIS, DIAGNOSIS, TREATMENT

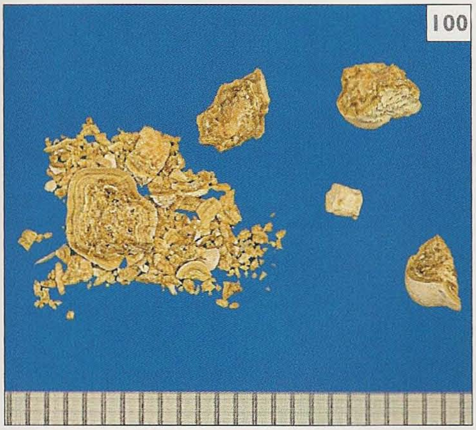
Drugs can appear as urinary stones if there is insufficient dilution of urine during prolonged, high-dose medication, or if there is backflow of urine into the kidneys or bladder. The drugs that are most commonly implicated as raw materials in the formation of urinary stones are the sulphonamides and sulfadiazine.[45,64] Only a small proportion of stones are found to be drug-induced on analysis. One European study found four sulphonamide stones (0.1%).[8] For anatomical reasons, males are found to have these stones more often than females, and affected dogs tend to be older.

Most drug-induced stones are not radiopaque, but can be detected using ultrasonography or double-contrast radiography.

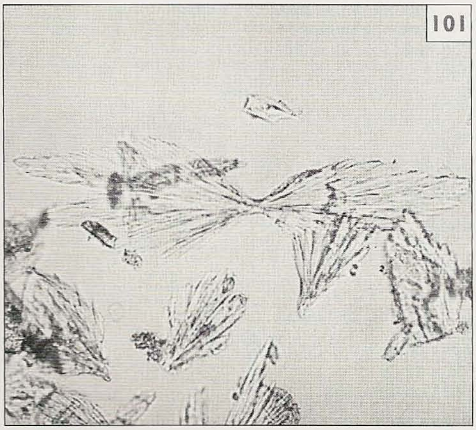
Analysis of drug-induced urinary stones is possible with infrared spectrometry (**102**). In the author's experience, infrared spectrometry occasionally reveals small quantities of sulfadiazine in calcium oxalate stones, suggesting treatment for infection or prophylaxis.

It is not possible to dissolve these stones; they should be physically removed using urohydropropulsion or surgery.

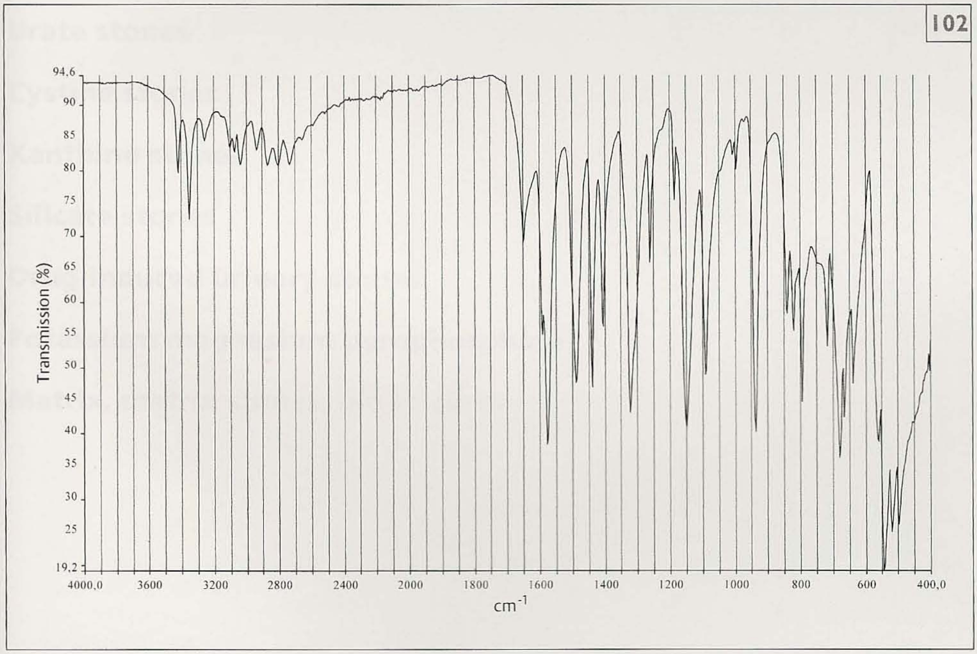
To prevent the recurrence of drug-induced urinary stones, the drug should be discontinued or replaced with a different substance. Where this is not possible, the dose may be reduced and the urine diluted by feeding an appropriate diet and mixing with water.



100 Fragments of a sulfadiazine stone from a dog.



101 Sulfadiazine crystals in urinary sediment.[45]



102 Infrared spectrum of sulfadiazine.

Hospital Veterinário de Trás-os-Montes

CHAPTER 3

Urinary stones in cats

Feline lower urinary tract disease

Struvite stones (magnesium ammonium phosphate hexahydrate)

Calcium oxalate stones

Calcium phosphate stones

Urate stones

Cystine stones

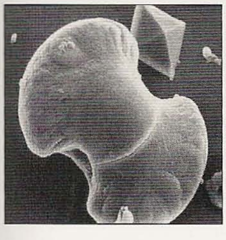
Xanthine stones

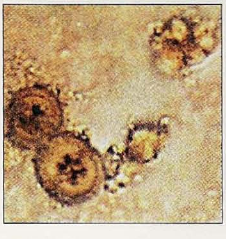
Silicate stones

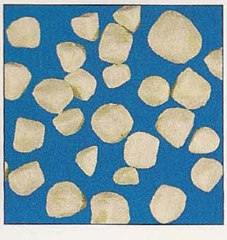
Drug-induced urinary stones

Potassium magnesium pyrophosphate

Matrix, matrix stones, blood clots







Feline lower urinary tract disease

INTRODUCTION

Previously, cats with lower urinary tract disease (dysuria, pollakiuria, stranguria, haematuria) were said to have FUS. However, this term should not be used as a diagnosis for a condition whose aetiopathogenesis varies so widely, since a broad range of causes produce the same clinical signs, and only part of the urological tract is affected. In this disorder, all of the clinical signs are restricted to the lower urinary tract, veterinarians in English-speaking countries have therefore coined the term 'feline lower urinary tract disease' (FLUTD) – although this too has a wide range of possible causes (*Table 35*).

> Since dysuria, stranguria, and pollakiuria can have different causes, but are confined to the lower urinary tract, the term FUS is obsolete.

The idiopathic form of FLUTD can be only diagnosed by elimination, after all other possible causes have been carefully and systematically excluded.[233]

EPIDEMIOLOGY

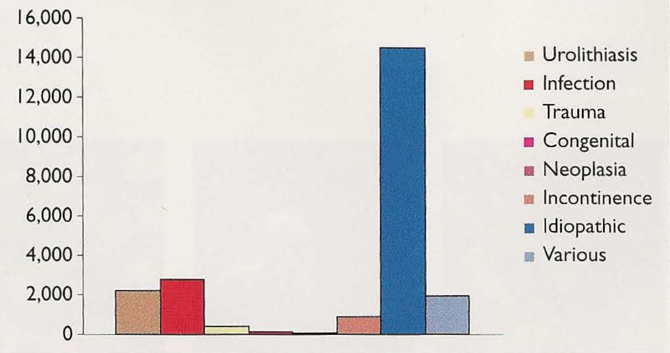
The incidence, i.e. the first-time appearance of illness in the total population, is given as 0.5–1.0% for lower urinary tract disease in cats.[234,235] Lower urinary tract disease was the presenting condition in 6.9% of >200,000 cats in veterinary consultations in the USA over a period of 13 years (1980–1993). In >95% of these cases, only five different diagnoses were made (*Table 36*).[236] However, two of these frequently made diagnoses are not aetiopathogeneses, but merely descriptions of clinical signs. Although in a follow-up study of 22,908 cats with lower urinary tract signs, the idiopathic form is still the most common, many other causes have now been identified (**103**).[15] In a prospective study, a specific diagnosis was found for 66 (46%) of 143 cats with lower urinary tract signs, the remainder had idiopathic FLUTD (*Table 37*).[237] Since the

Table 36 Diagnoses of lower urinary tract symptoms in 15,349 cats (1980–1993).[236]

Diagnosis	Number	Percent
Feline urological syndrome (FUS)	5,262	34.3
Non-specific cystitis	4,566	29.8
Obstructed urethra	3,355	21.9
Stone in urethra	1,171	7.6
Stone in bladder	718	4.7

Table 37 Prospective study to evaluate the causes of lower urinary disease in 143 cats.[237]

Cause	Number	Percent
Idiopathic	77	53.8
Urinary tract plug	32	22.4
Urinary stones	30	21.0
Urinary stone and urinary tract infection	2	1.4
Bacterial urinary tract infection	2	1.4



103 Diagnoses of 22,908 cats with lower urinary tract signs in a study from the USA (1980–1997).[15]

Table 35 Causes of FLUTD.

Cause	**Examples**
Inflammation	
Infectious	Viruses (feline calicivirus?; feline syncytia forming virus?)
	Bacteria (*Escherichia coli*; *Staphylococcus* spp; *Streptococcus* spp; *Pasteurella* spp; etc.)
	Fungi (*Candida* spp; *Aspergillus* spp; *Trichosporon* spp)
	Parasites (*Capillaria feliscati*)
	Mycoplasma and ureaplasma (*M. felis*; *M. gatae*; *Ureaplasma* spp)
Noninfectious	
Trauma	
Neurogenic disorder	Urethral spasm
	Reflex dyssynergia
	Overdistension of the bladder (secondary to obstruction)
Anatomical problems	
Congenital	Urachal fistula
	Persistent paramesonephric ducts (uterus masculinus)
	Ectopic ureter
	Urethrorectal fistula
	Phimosis
Acquired	Constricted urethra
	Urethrovaginal fistula
Metabolic disorders	
Bladder stones	Struvite stones
	Calcium oxalate stones
	Calcium phosphate stones
	Urate stones
	Other stones
Urinary tract plugs	
Neoplasia	
Malignant	Transitional cell carcinoma
	Squamous cell carcinoma
	Adenocarcinoma
	Haemangiosarcoma
	Lymphoma
	Myxosarcoma
	Prostatic adenocarcinoma
	Unclassified carcinoma
Benign	Cystadenoma
	Leiomyoma
	Fibroma
	Haemangioma
	Papilloma
Idiopathic	

risk of lower urinary tract disease in cats is strongly dependent on external conditions (breed, age, sex, living conditions, diet), epidemiological results should always be analysed in context.

> The idiopathic form is the commonest cause of lower urinary tract disease (FLUTD) in cats.

Bacterial urinary tract infections are rare in young cats, occurring in <2% of the animals presenting with FLUTD.[237,238] The probability of bacterial urinary tract infection increases with age; in cats over 10 years old, a positive bacterial urine culture was found in >45% of cats with lower urinary tract signs.[124] Two thirds of these cats had renal failure; the remaining third were suffering from a concurrent condition such as hyperthyroidism, treatment with corticosteroids or diuretics, urinary incontinence, neoplasia, or infection with feline leukaemia virus (FeLV) and/or feline immunodeficiency virus (FIV). A further risk factor for bacterial urinary tract infection is diabetes mellitus.[15,239] Recent placement of a urinary catheter also increases the risk of bacterial urinary infection.

> Urinary tract infections are rare in young cats (<5 years), but are more common in older cats (>10 years).

Urinary tract plugs are composed of a matrix with varying quantities of mineral. A range of different minerals may be found in these plugs (**104**), with struvite being by far the most significant. The proportion of struvite crystalluria in cats in a US study has remained largely unchanged over the years, and does not seem to reflect increased calcium oxalate in urine.[240]

PATHOGENESIS

Pathogenesis of urethral plugs

The anatomy of the lower urinary tract in tomcats (**105**) is such that plugs may become lodged at bottlenecks in the urethra. These plugs consist mainly of organic matrix (protein and polysaccharides), with small deposits of minerals that form urinary crystals (**106**). Firstly, inflammation (e.g. from viruses or bacteria) leads to the production of mucoproteins and inflammatory products, which then lead to haematuria and dysuria. Various viruses (e.g. calicivirus, bovine herpes virus 4) have been found in urethral plugs from tomcats. Secondly, crystalluria may lead to stone formation; struvite crystals are common in cats even without bacterial infection. Thirdly, the simultaneous occurrence of urinary tract inflammation and crystalluria may promote the formation of plugs of matrix and crystals, which may lead to urethral obstruction, especially in male cats. In rare cases, female cats may also produce urethral plugs. Over 80% of the mineral deposits are composed of struvite.[26] The risk factors for the appearance of a particular type of mineral in a urethral plug are presumably the same as those for urolithiasis with the corresponding mineral.

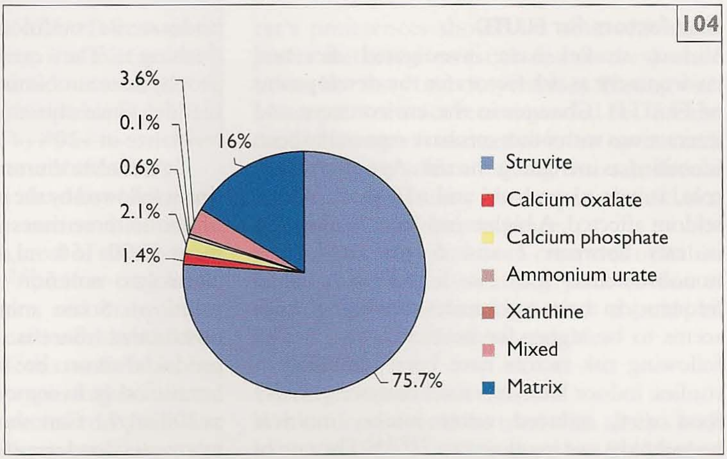
Pathogenesis of idiopathic FLUTD

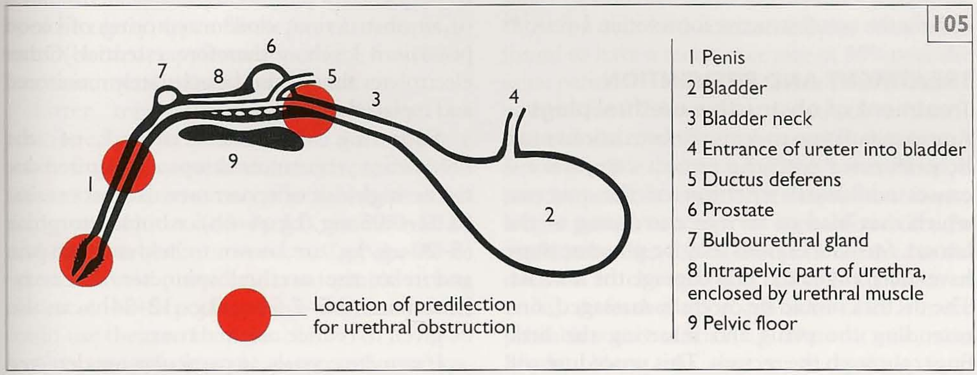
Idiopathic FLUTD, also called feline interstitial cystitis (in reference to human interstitial cystitis, which is associated with the same clinical signs), is a disease whose exact aetiology is not known. An inappropriate reaction to stress is thought to be a major co-factor.

When a trigger factor places stress on the CNS, the hypothalamo-hypophyseal-adrenal system and the sympathetic nervous system are activated. This stimulates the production of numerous hormones (including cortisol, catecholamine, neurosteroids) and other mediators.[241] It has been shown that in a stressful situation, cats with idiopathic FLUTD produce smaller quantities of stress hormones and are thus unable to manage stress appropriately. These animals also have a reduced glycosaminoglycan layer coating the urothelium that lines the bladder. This means that the underlying nerve endings (unmyelinated pain fibres) have reduced protection, with the local release of substance P.[239] This increases the permeability of the bladder and promotes the release of local inflammatory products (nitrogen monoxide). Petechial haemorrhages in the mucosa, release of protein into the urine, and the classic clinical signs (dysuria, stranguria, pain) then follow.

It is assumed that a genetic predisposition or an intrauterine change during the fetal stage, or a combination of both, is responsible for the onset of idiopathic FLUTD.[241] Idiopathic FLUTD often appears in conjunction with other conditions, such as obesity or hypertrophic cardiomyopathy.[241]

104 Mineral components of 1,050 urinary tract plugs in a US study.[237]

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1
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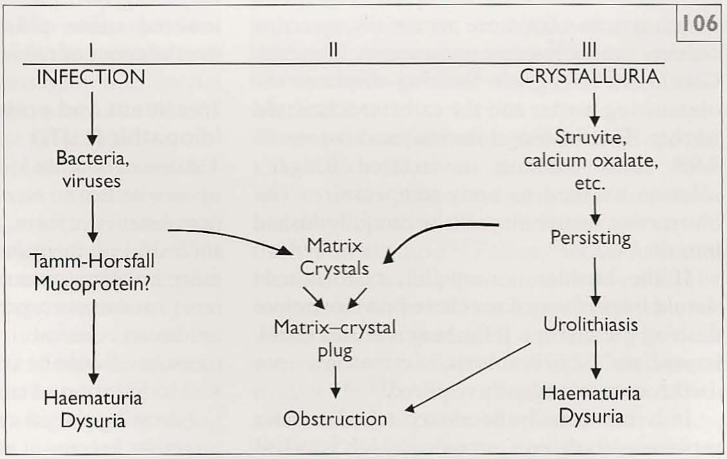
Location of predilection for urethral obstruction
1 Penis
2 Bladder
3 Bladder neck
4 Entrance of ureter into bladder
5 Ductus deferens
6 Prostate
7 Bulbourethral gland
8 Intrapelvic part of urethra, enclosed by urethral muscle
9 Pelvic floor

105 Schematic drawing of the lower urinary tract of a tomcat.

106 Schematic drawing of the different manifestations of FLUTD – see text for details (modified from Buffington).[13]


106
I
INFECTION
Bacteria, viruses
Tamm-Horsfall Mucoprotein?
Haematuria Dysuria
II
Matrix Crystals
Matrix–crystal plug
Obstruction
III
CRYSTALLURIA
Struvite, calcium oxalate, etc.
Persisting
Urolithiasis
Haematuria Dysuria

Risk factors for FLUTD

Various studies have investigated diet and environment as risk factors for the development of FLUTD. Changes in the environment and interactions with other cats have repeatedly been identified as increasing the risk. Age also plays a role, as cats <1 year old and >10 years old are seldom affected. A higher incidence is observed in cats between 2 and 6 years old. The nonobstructive form is found with equal frequency in males and females, although the risk seems to be higher for neutered cats.[234] The following risk factors have been identified in studies: indoor lifestyle, raised bodyweight, dry food diet, reduced water intake, multicat households, and longhair cats.[239,242] The rate of recurrence for obstruction is 45% in males,[243] and 39% for the nonobstructive form within 1 year.[244]

TREATMENT AND PREVENTION

Treatment of obstructive urethral plugs

Any manipulation to remove obstructions must be performed with the utmost care, since it causes additional irritation of the mucosa, which may lead to further narrowing of the lumen. Struvite crystals may be present; these have sharp edges and may damage the mucosa. The urethra should be carefully massaged, first extruding the penis and inserting the little finger through the rectum. This procedure will generally require the cat to be sedated or anaesthetized (see Chapter 1).

If the distal end of the urethra is clear and the obstruction lies more proximally, a narrow catheter may be inserted using aseptic lubricant. Continued retrograde flushing displaces the obstructing matter and the catheter is inserted further. The flushing solution used is a sterile 0.9% saline solution or lactated Ringer's solution warmed to body temperature. The obstructing matter may also be carefully flushed into the bladder.

If the bladder is very full, cystocentesis should be performed to relieve pressure before flushing the urethra. If flushing is unsuccessful, immediate cystocentesis, cystotomy or urethrotomy is urgently required.

It is not usually necessary to administer antibiotic prophylaxis, provided a high standard of cleanliness has been maintained. As stated previously, bacterial urinary infections are rare in young cats, however a bacteriological culture should always be taken from urine collected under sterile conditions (i.e. prior to retrograde flushing). The cat should not be given prophylactic antibiotics while a catheter is in the bladder since this causes bacteria to develop resistance in >20% of cases.

To stimulate diuresis, removal of the obstruction is followed by the intravenous administration of two to three times the maintenance requirement (100–150 ml/kg/day) of an isotonic electrolyte solution (e.g. lactated Ringer's solution). Some animals may develop post-obstructive diuresis. The volume of urine produced must be monitored and replaced intravenously. In some cases, this may be as much as 200 ml/hr. Care should also be taken because many cats develop profound hypokalaemia as a consequence of diuresis, especially after removal of an obstruction; close monitoring of blood potassium levels is therefore essential. Other electrolytes should also be accurately monitored and replaced where necessary.

Following definitive removal of the obstruction, regular check-ups are required due to the high risk of recurrence. Acepromazine (0.02–0.05 mg/kg q4–6h) or buphrenorphine (5–20 μg/kg) are known to help manage pain and relax the urethral sphincter. Phenoxybenzamine (2.5–7.5 mg/kg q12–24h) can also be given to reduce urethral tone.

If struvite crystals, in particular, are detected in matrix–crystal plugs (always send off for analysis) a special struvite stone prevention diet may be given. Care must be taken that the lowered urine pH does not lead to the development of calcium oxalate crystals.

Treatment and prevention of idiopathic FLUTD

Treatment of acute idiopathic FLUTD depends upon whether an obstruction is present. In the nonobstructive form, diuresis and analgesia are successful on their own in the acute stage. The more important issue is the adoption of long-term measures to prevent recurrence and to minimize clinical signs. The following measures should be considered:

- Modification of environmental factors (allowing the cat outside, making it more active, keeping it occupied, avoiding competition with others).
- Dietary measures (including measures to increase the quantity of urine).
- Medication.

A good understanding of FLUTD by owner and veterinary surgeon is at least as important as prophylactic measures in preventing recurrence of idiopathic FLUTD.

Modification of environmental factors

The first, and sometimes the most important measure, is to make the environment more interesting, complex and, most of all, tolerable to the individual cat.[241,245] Litter tray, litter, food bowls, type of water, and many other components of a typical cat's world should be selected to ensure the cat feels comfortable. For instance, a variety of litter types may be offered initially to identify that preferred by the cat. The cat should also be allowed to choose the other accessories in its everyday life: covered or open litter tray; type of litter (smell, clumping); water (bottled, tap, from dispenser); food bowl (ceramic, metal, plastic), and so on.

Litter tray and food bowl must be positioned so that the cat can use them in peace (away from busy areas and children). Sudden noises (fans, driers) may startle the cat. Cats living in multicat households should not be unduly disturbed by other cats. Care should be taken to avoid providing comfortable sitting places at bottlenecks where dominant cats could use them to keep guard.

Cats are very clean creatures, so litter trays, food dishes, and drinking bowls should always be kept clean. In particular, the smell of ammonia in a covered litter tray may put the cat off using it, which may lead to urine retention. If cats have urinated outside the tray, the area must be cleaned very thoroughly with special enzyme cleaners so that the same or other cats are not attracted to urinate there again.

In multicat households, care should be taken to ensure that all cats have equal access to preferred resting, eating, and toilet locations. The 1+ rule must be strictly followed. This means that for all items necessary for everyday life (litter tray, sleeping place, water bowl) one more is provided than there are cats in the household. Particular care should be taken to see that all cats are simultaneously able to find what they would consider a high-quality resting place: for example there must be adequate provision of window seats or armchairs.

It is important that the owner pay attention to the cats several times a day, either with typical cat toys (e.g. ball) or with food. Here too, the cat's preferences should be observed: some prefer feathery toys (stick and feather) while others like furry ones (toy mouse). Playing with a laser pointer is not recommended because the cat can become frustrated as it can never catch it. It also goes without saying that cats should have the opportunity to sharpen their claws, climb, hide, and sleep in peace.

Cats, on the whole, are creatures of habit. Changes to their routine (e.g. place or time of feeding) can be stressful and should be introduced as gradually as possible.

Dietary measures

Wet cat food should be tried with all cats with idiopathic FLUTD. Cats given wet food had an 11% FLUTD recurrence rate within 1 year, while those on standard commercial dry food were found to have a recurrence rate of 39% over the same period.[246] In addition, water can be mixed with the food to keep the concentration of matrix material and crystalline substances in the urine as low as possible. If the cat will only eat dry food, it may be possible to add more liquid to it over a longer period, or to opt for a specialized diet. As explained earlier, the cat should be involved in the decision to change food (offer both foods at once). A further approach is to offer a more palatable source of fluid (e.g. dilute cat milk, meat broth). Many cats also enjoy drinking from indoor fountains or from the tap.

There is no proof that struvite crystals damage the normal urothelium or aggravate existing cystitis.[239]

Medication

Pheromones are fatty acids that transmit specific information between animals of the same species. It is not known exactly how they work, but they appear to affect the limbic system and the hypothalamus.[247] Feliway® (CEVA Animal Health) is a facial pheromone licensed for the treatment of behavioural problems in cats, which has demonstrated a positive effect on some cats with idiopathic FLUTD in several studies.[248,249] In a placebo-controlled, randomized, double-blind crossover study, Feliway® or a placebo was used for 2 months on nine cats with severe recurrent idiopathic FLUTD. While no effect was observed in four cats, the other five showed significant improvement while on Feliway®.[250]

> In idiopathic FLUTD there is no reason to acidify the urine to avoid struvite crystal formation.

Amitriptyline, a tricyclic antidepressant, has been used with partial success in humans with interstitial cystitis. Amitriptyline does not appear to have any short-term therapeutic effect;[251,252] over a year, however, severe idiopathic FLUTD clinical signs were significantly reduced in 9 out of 15 cats given amitriptyline (10 mg orally q24h).[253] Side-effects are rare, but decreased voiding has been reported. An initial dosage of 2.5–12.5 mg/cat is gradually increased until a mild sedative effect is achieved. If no improvement is detectable after 4 months, amitriptyline may be gradually discontinued. Sudden cessation can lead to acute flare-up of clinical signs.[252]

Orally administered *glycosaminoglycans* are excreted in the urine and settle on the damaged urothelium, protecting it. In humans, glycosaminoglycans have been successfully used to treat interstitial cystitis. In cats with FLUTD, the glycosaminoglycan level in urine is significantly lower than in healthy cats.[254] Anecdotal reports claim a reduced rate of recurrence in individual cases with FLUTD after the administration of 50 mg glycosaminoglycan per cat twice a day,[239] but a placebo-controlled double-blind study found no significant difference in recurrence between the administration of 125 mg N-acetyl glucosamine and a placebo over a period of 6 months with 20 cats per group.[255] A whole range of other drugs has been tried, mostly without success, in cats with idiopathic FLUTD:[233]

- Antibiotics should only be used for bacterial cystitis.[256]
- Urinary tract antiseptics (e.g. methylene blue) are contraindicated in cats.
- The use of phenazopyridine as a urinary tract analgesic is contraindicated in cats.[257]
- Smooth muscle and skeletal muscle antispasmodics: propantheline showed no reduction in recurrence compared to the control in a clinical trial.[256] However, in cats with acute, nonobstructive FLUTD, propantheline (7.5 mg/cat orally every 3 days) can reduce the severity of dysuria. Diazepam should not be given to nonobstructed cats because of the danger of hepatic insufficiency.
- Prednisolone has no short-term or long-term positive effect.[258] It should not be used in cats with urinary catheters.

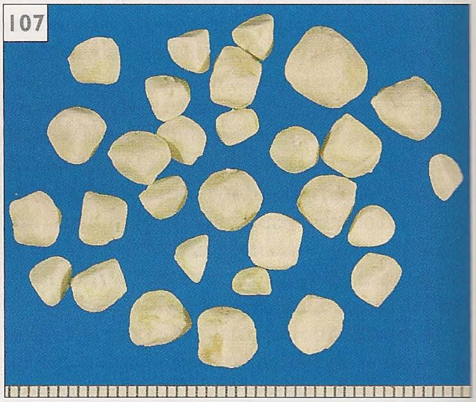
Struvite stones (magnesium ammonium phosphate hexahydrate)

INTRODUCTION

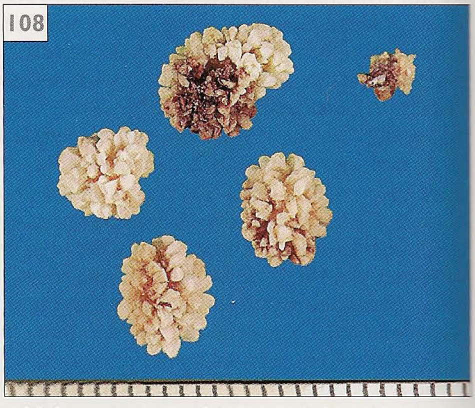
Struvite stones in cats are externally very similar to stones of the same composition in other species. The stones are white to grey and can present as multiple small stones or as large single stones (**107, 108**).

EPIDEMIOLOGY

In the 1980s, over 80% of urinary stones in cats were composed of struvite.[27,259,260] The proportion of struvite stones dropped considerably over subsequent decades (**109**);



107 Struvite stones from a cat, multiple bladder stones, smooth surface.



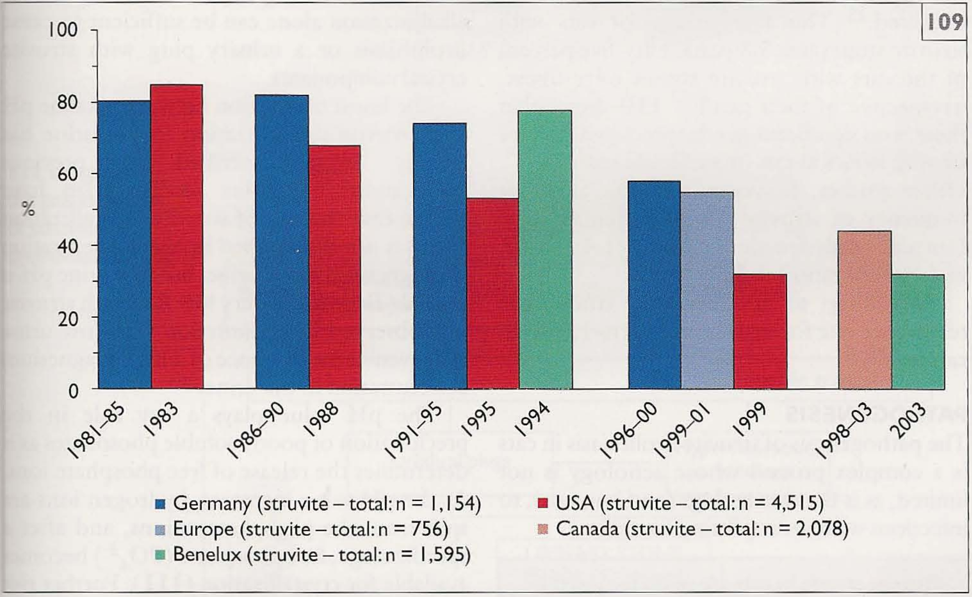
108 Struvite stones from the bladder of a cat, sharp-edged surface.

the number of calcium oxalate stones found in cats has increased steadily.

Varying percentages of struvite stones can be observed in individual European countries (*Table 38*). These variations are also indications of the causes for the formation of struvite stones, as a function of differences in living conditions and diet in different regions. Breed distribution in the various countries also plays a significant role in these statistics.

> Over recent years, the proportion of struvite stones in cats has decreased significantly in favour of calcium oxalate stones.

In a European study, more than 20 cat breeds with urinary stones were found (see Chapter 1). Struvite stones were primarily diagnosed in European Shorthairs and Persians (*Table 39*). An American study found the highest frequency of struvite stones in Persian,



109 Changes to the percentage occurrence of struvite stones in cats at various time periods and regions.[8,24a,25,26,78]

Table 38 Percentage distribution of struvite stones in various European countries (1999–2001).[8]

Country (total stones)	**(%)**
Italy (n = 81)	79.0
Austria (n = 41)	73.2
Finland (n = 53)	71.7
France (n = 51)	58.8
Germany (n = 749)	57.3
Netherlands (n = 199)	41.7
Switzerland (n = 91)	35.2

Table 39 Frequency of struvite stones in various cat breeds in Europe.[8]

Breed (total stones)	**(%)**
European Shorthair (n = 1,119)	68.1
Persian (n = 449)	59.0
Chartreux (n = 27)	44.4
Siamese (n = 26)	46.2
Other (n = 176)	58.5
Total (n = 1,797)	**64.2**

Himalayan, and Siamese cat breeds.[261] A Canadian study shows that struvite stones are most frequent in Himalayans, Persians, and Siameses.[26] The analysis of more than 17,000 urinary stones in cats has shown that Chartreux, various Shorthair, Himalayan, and Ragdoll cats display an increased risk of developing struvite stones.[25]

In Europe, struvite stones are evenly distributed between male and female cats; many animals are neutered (**110**). In the USA female animals (58%) are marginally more affected by this disease, and most of the cats (91%) were neutered.[25] The average age of cats with struvite stones was 5.8 years. Fifty-five percent of the cats with struvite stones were obese, irrespective of their gender. **110** shows that there is no significant gender predisposition for struvite stones in cats (male:female ratio 1.1:1). Other studies, however, describe a higher frequency of struvite stones in female cats: Canada male:female ratio 1:1.4; USA male:female ratio 1:1.5.[15,26,261]

According to a European study, the recurrence rate for struvite stones (n=1,078) in cats is 28%.[8]

PATHOGENESIS

The pathogenesis of struvite urolithiasis in cats is a complex process whose aetiology is not limited, as is the case in dogs (and humans), to infections with urea-splitting bacteria.

> Struvite stones in cats are seldom caused by urea-splitting bacteria in urine. Sterile urolithiasis is the most usual occurrence.

As a rule, micturition in cats occurs at long intervals. Many only urinate once a day and some only every 2–3 days. Ambient temperature and fluid intake play a significant role. It has been demonstrated that cats – unlike dogs – do not compensate for diets with a low moisture content by drinking more water.[262] Instead, they simply produce a smaller volume of highly concentrated urine. Originally desert animals, cats also have long loops of Henlé and are able to concentrate urine to a high degree. The specific gravity of urine can increase to >1.060. These aetiological factors mean that cats living in urban households in particular are susceptible to diseases of the lower urinary tract.

A urethral obstruction can cause urine retention in the bladder or concentrated urine and, in rare cases, encourage infections. Some years ago dry cat food contained large quantities of calcium, magnesium, and phosphate; the urine was already mildly alkaline (above pH 7.0) and this led to rapid struvite crystallization. Ad libitum feeding, a common practice with dry foods, can increase urine pH throughout the day and lead to latent supersaturation of the urine with struvite even without an infection with urea-splitting bacteria. The postprandial waves of alkalinization alone can be sufficient to cause urolithiasis or a urinary plug with struvite crystal components.

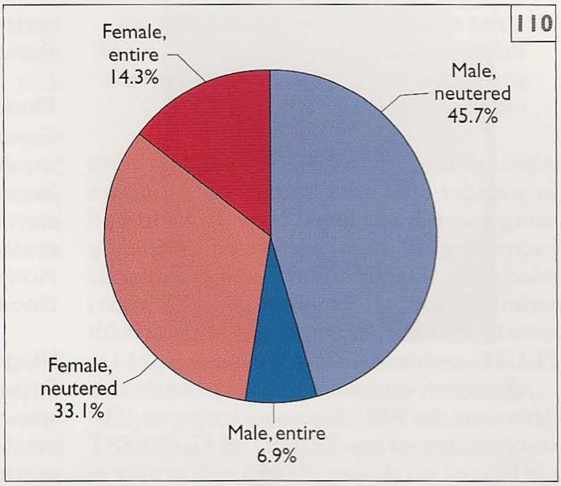
The linear correlation between alkaline pH and struvite crystallization in cat urine has already been described in previous publications.[263] Earlier feeding trials have shown that the risk of struvite crystallization (RSS) is not determined by the concentration of magnesium in the urine, but that urine pH is crucial (*Table 40*). A very low RSS with struvite was observed in conjunction with low urine pH, even in the presence of a high magnesium concentration in the urine.[264]

The pH value plays a key role in the precipitation of poorly soluble phosphates as it determines the release of free phosphate ions. As the pH value increases, hydrogen ions are split from the phosphate anions, and after a specific stage, free phosphate (PO_4^{3-}) becomes available for crystallization (**111**). Further risk factors for the formation of struvite crystals include the moisture content of food, general fluid intake, and urine concentration. The main indicator in assessing the risk of struvite stone production is the RSS value.

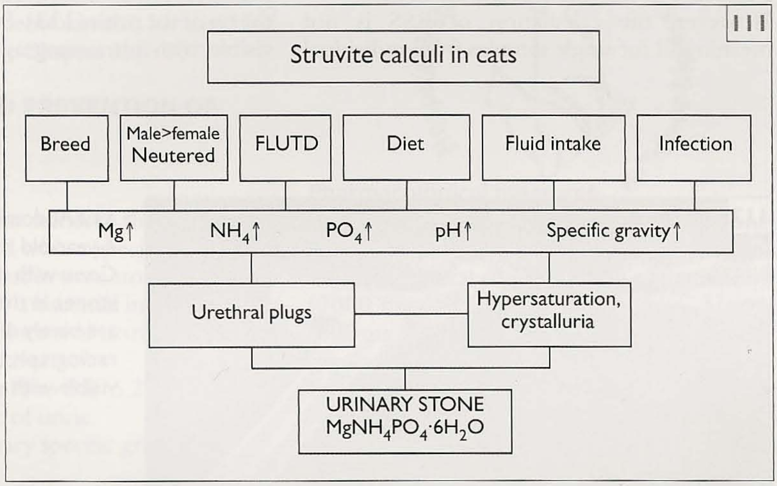
$$H_2PO_4^{1-} \xrightarrow[\text{- H+}]{} HPO_4^{2-} \xrightarrow[\text{- H+}]{} PO_4^{3-}$$

$$\xrightarrow[\text{increasing pH value}]{\hspace{8em}}$$

Infection-induced struvite stones can also occur in cats, with the same pathogenesis as in dogs (see Chapter 2). They are much rarer than sterile struvite stones because cats have a very effective natural defence against bacterial infection of the urinary tract. An underlying cause is usually responsible for bacterial infections of the urinary tract in cats, for



110 Gender distribution of cats with struvite stones (total n = 1,797, struvite stones n = 1,154).[8]


111
Struvite calculi in cats
Breed
Male>female Neutered
FLUTD
Diet
Fluid intake
Infection
Mg↑
NH_4↑
PO_4↑
pH↑
Specific gravity↑
Urethral plugs
Hypersaturation, crystalluria
URINARY STONE $MgNH_4PO_4 \cdot 6H_2O$

111 Diagram of the pathogenesis of struvite urolithiasis in cats.

instance an obstruction of the urinary tract, renal failure, urinary stones, FLUTD or tumours. Significant iatrogenic causes include urinary catheterization or a perineal urethrostomy (short, wide urethra).

DIAGNOSIS

Urinalysis

- pH: mostly >7.2, measure more than once a day if appropriate.
- Specific gravity: frequently >1.030.
- Nitrite on dipsticks: not reliable in cats.
- Urine dipsticks with struvite stones: frequently positive for protein and haemoglobin/erythrocytes.

Table 40 Effects of different diets on the pH value, magnesium concentration, and relative struvite supersaturation in cat urine.[264] (MgO = magnesium oxide)

Urine values	Standard diet	+ $MgCl_2$	+ MgO
pH	7.8 ± 0.3	5.8 ± 0.1	7.9 ± 0.3
Mg (mmol/l)	7.3 ± 2.8	53.1 ± 16.3	49.1 ± 14.1
Relative super–saturation (struvite)	24.7	0.7	1.9

- Urine sediment: characteristic coffin-lid-shaped crystals (**29**) (not definite proof of struvite stones!); copious urinary gravel is often observed.

Although urinary tract infections seldom occur in younger cats, urine should be withdrawn using a sterile technique (cystocentesis) and bacteriological tests performed, including microbial identification and antibiotic sensitivity testing. In older cats (>8 years) urinary tract infections in conjunction with FLUTD are found in 25% of cases.

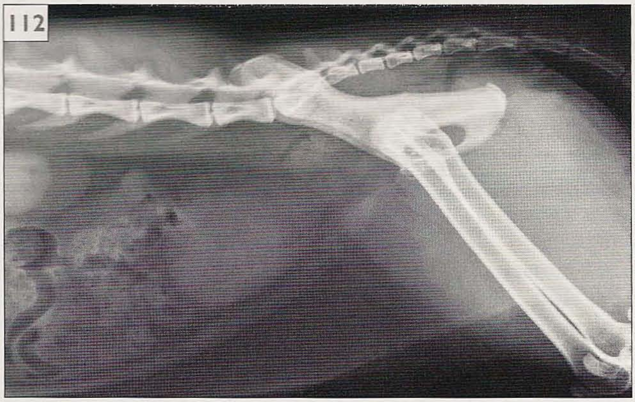
Quantitative urine analyses are required to determine the RSS of urine with struvite. The computer programs EQUIL or SUPERSAT can be used to calculate the RSS with struvite as a measure of the risk of stone formation.[94,158] However, the calculation of RSS is not meaningful for single samples from individual patients, but is used in the development of therapeutic diet food.

Blood tests

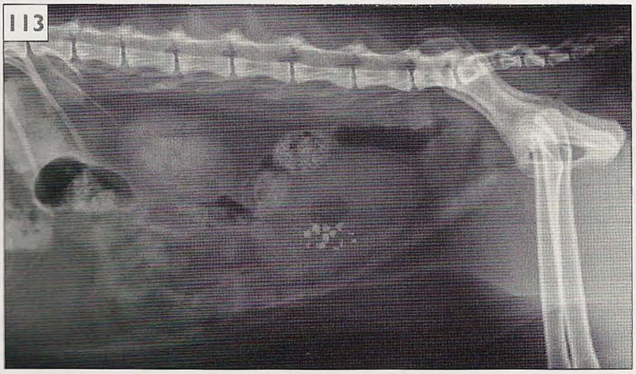
Cystitis caused by struvite stones does not usually induce inflammatory changes on the haematological profile. Biochemical changes are only observed if struvite stones result in renal failure or if an obstruction is present. Normally there are no pathological findings on blood biochemistry.

Diagnostic imaging

Struvite stones are usually radiopaque and can be seen clearly along the entire urinary tract. In the event of inconclusive results, contrast radioscopy may be necessary (**112**). It is imperative to image the whole urinary tract including the urethra and the tip of the penis (**113**). Stones are also clearly visible with ultrasonography, thanks to their



112 Abdominal radiograph of a 4-year-old male neutered Maine Coon with multiple struvite stones in the bladder. The stones are barely distinguishable in the radiograph, but are clearly visible with ultrasound.



113 Radiograph of a male European Shorthair with multiple small bladder stones. (Photograph by Dr C. Stengel, Hofheim.)

characteristic acoustic shadow. Sometimes it can be difficult to distinguish small stones from gravel – cystoscopy can prove helpful in such cases (**114**).

The penis should always be assessed as part of an imaging examination; in the presence of obstruction, it is frequently possible to see or feel blockages at its distal extremity (**25**). These are usually soft, sandy, and can sometimes be massaged out of the urethra.

Urinary stone analysis

A precise analysis of the urinary stones is essential for the instigation of a specific therapeutic protocol following the removal of urethral blockages or urinary stones. All mineral and organic components can be identified using infrared spectrometry. Mixed stones consisting of different components can also be identified with confidence. See Chapter 1, p. 30.

TREATMENT AND PREVENTION OF RECURRENCE

Treatment

Dietary measures

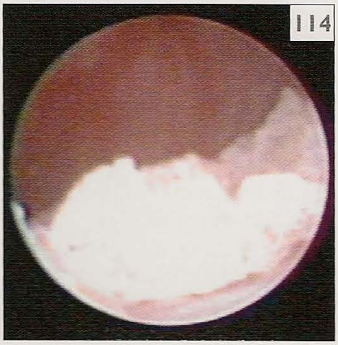
Symptomatic struvite stones in the bladder can usually be dissolved with a special diet. Note that more than 70% of struvite stones in cats are not accompanied by a bacterial infection.[14]

The dietary dissolution of struvite stones has the following objectives:

- Decrease urine pH to 5.8–6.2.
- Increase volume of urine.
- Reduce the urinary specific gravity to <1.030.
- Reduce the intake of lithogenous substances – magnesium, calcium, phosphate.

Sterile struvite stones were successfully dissolved within 14–141 days (average 36 days) following the administration of moist foods with a reduced magnesium content that result in a urine pH of approximately 6.0.[265,266] The sodium content of commercial foods administered to dissolve struvite stones is raised to encourage fluid intake and increase diuresis. Commercial foods are now available that very effectively influence the composition of urine to aid in the dissolution of struvite stones in cats.

> Successful dissolution of struvite stones in cats requires the urine pH to be <6.5.



114 Cystoscopy of bladder stones from the cat in **113**. The stones were surgically removed and analysis proved them to be 100% struvite. (Photograph by Dr. C. Stengel, Hofheim.)

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Pharmacological measures

If cats refuse to eat the mildly acidifying, stone-dissolving diet, acidification can be encouraged through the oral administration of methionine (1000 mg/cat/day) or ammonium chloride (800 mg/cat/day). Blood gas must be checked regularly to avoid metabolic acidosis, otherwise there is a risk of bone demineralization and hypercalcaemia.[80,267] Other side-effects associated with methionine include anorexia, ataxia, cyanosis, methaemoglobinaemia, and Heinz body anaemia. A significant complication is the formation of calcium oxalate stones. Additional pharmacological acidification is contraindicated in cats on an acidifying diet.

> Drugs for urine acidification must not be administered together with an acidifying diet.

In addition to dietary measures, infection-induced struvite stones must be treated with appropriate antibiotic therapy (ideally following antibiotic sensitivity testing). Both the diet and antibiotic should be administered for 4 weeks after the stones can no longer be detected by radiography or ultrasonography. In three cats with *Staphylococcus*-induced struvite stones the dissolution took between 64 and 92 days.[265]

Further measures

Urohydropropulsion may be used instead of dietary dissolution for small bladder stones. If no reduction in stone volume is observable after 2 months on a strict diet and controlled acid (<6.3) urine pH, then chemolysis should be discontinued and symptomatic struvite stones surgically removed.

Prevention of recurrence

Dietary and pharmacological measures should be continued for a further 4 weeks after imaging examinations no longer show any stones in the bladder. Measures for dissolving the stones should then be reduced, as there is the danger of systemic disease resulting from long-term urine acidification. This is particularly important in young animals, whose bone growth is not yet complete. A heavily acidifying diet also increases the risk of calcium oxalate stones.

Commercial foods have been developed with the RSS value calculated for use both in struvite and calcium oxalate stone prophylaxis.[158,176] These diets provide a moderate increase in sodium intake to encourage fluid intake and thus reduce the specific gravity of the urine; the target is a specific gravity of <1.030.

Following successful treatment, cats with FLUTD and struvite stones should be examined every 3 months for possible recurrence, even if they do not present with any clinical signs.

General measures for the prevention of recurrence

- Support diuresis: clean water *ad libitum*, add water to food.
- Use moist food if possible; alternatively offer moistened dry food or a special prophylactic food.
- Provide optimal conditions to encourage regular urination, clean cat litter (1+ rule).
- Increase physical activity.
- Avoid excess bodyweight.
- Avoid stress factors.
- Do not administer furosemide.
- Regular monitoring with ultrasonography or radiography.
- In mixed stones it is important to detect special genetic abnormalities e.g. cystine, urate or xanthine in the urine as the primary cause of stone formation.

Calcium oxalate stones

INTRODUCTION

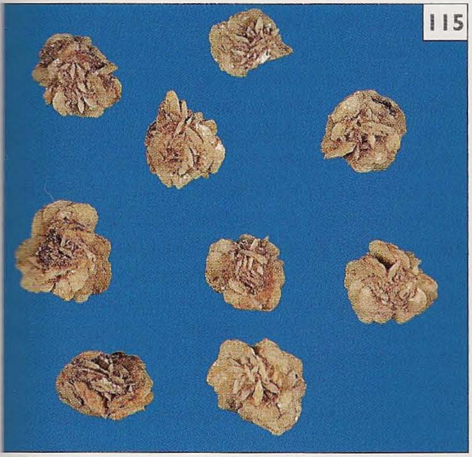
Calcium oxalate stones have the same shape and colour in both cats and dogs (**115, 116**). They are typically small and multiple. Whewellite (calcium oxalate monohydrate) stones are very hard and brown to black in colour. The surface is smooth and often has mulberry-shaped growths on which sharp-edged weddellite crystals can form.

Weddellite (calcium oxalate dihydrate) stones have a looser structure of pointed, sharp-edged individual crystals. The crystals are mostly pale yellow in colour, but can also be dark brown with encrusted blood.

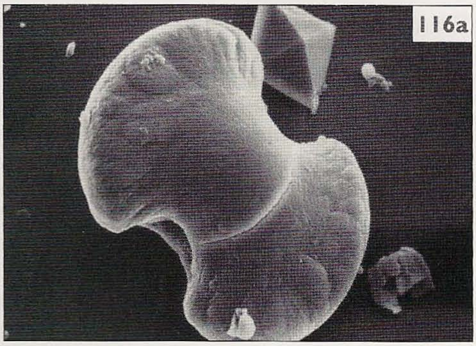
EPIDEMIOLOGY

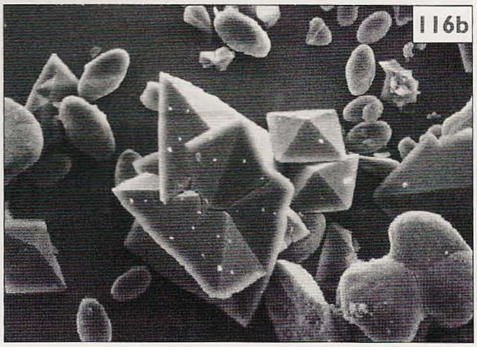
Calcium oxalate stones in cats were very rare in the early 1980s and the focus was on treating struvite stones.[236,259,260] A steady increase in the incidence of calcium oxalate stones was seen over the following years, initially in the USA, then also in other countries, and today they can represent more than 50% of urinary stones in cats (**117**).

> Calcium oxalate stones represent between 30 and 60% of all urinary stones in cats today, depending on the study.

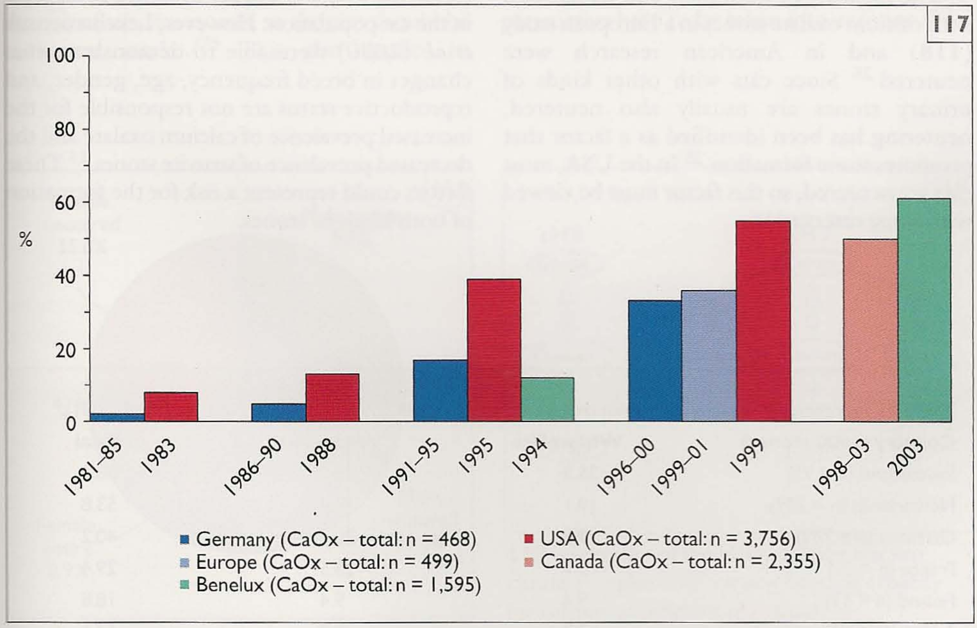


115 Calcium oxalate stones from a cat.





116 Calcium oxalate crystals in urine sediment. (**a**) Dumbbell-shaped whewellite crystal (scanning electron microscope image). (**b**) Weddellite microcalculus, whewellite crystal (dumbbell shaped), and weddellite crystals (bipyramids) (scanning electron microscope image).



117 Percentage change in calcium oxalate stone frequency in cats in various time periods and regions.[8,25,26,78]

There are significant differences between the frequency of calcium oxalate stone in various countries. In Europe, for instance, very high percentages of calcium oxalate stones in cats (>58%) have been observed in the Netherlands and Switzerland (*Table 41*), whereas in Italy they only account for 11% of all urinary stones.[8] Regional differences are also seen in terms of the relative prevalence of the two phases of calcium oxalate. A European study shows a slightly higher frequency for weddellite stones compared with whewellite stones (*Table 41*). In the USA, on the other hand, whewellite appears much more frequently in urinary stones in cats than weddellite (whewellite:weddellite = 5.6: 1).[236] Other authors do not distinguish between whewellite and weddellite.[26,268]

The breeds that most frequently have calcium oxalate stones in Europe are the European Shorthair and Persian. Chartreux are particularly predisposed to the formation of calcium oxalate stones. According to studies from the USA, the risk of calcium oxalate stone formation is higher in Burmese, Persians, and Himalayans.[261,269] Canadian studies indicate that calcium oxalate stones are commonest in Himalayans, Persians, and Siamese.[26]

The majority of both male and female cats with calcium oxalate stones in a European study (**118**) and in American research were neutered.[25] Since cats with other kinds of urinary stones are usually also neutered, neutering has been identified as a factor that promotes stone formation.[25] In the USA, most cats are neutered, so this factor must be viewed with some reservation.

On average, cats with calcium oxalate stones are older (7.5 years) than cats with struvite stones (5.8 years) when they first develop the disease.[25,269] Cats in the age range ≥7 to <10 years have the highest risk of developing calcium oxalate stones.[25]

The majority of calcium oxalate stones in a European study came from animals with the first occurrence of disease (73%), the remainder were recurrences. Of the cats in this study, 44% were classified as obese. Other publications have also identified excessive weight as a factor that predisposes cats to urinary stones.[26,256,269-271] The increase in obesity in the cat population – the most frequent dietetic problem in cats today – to more than 25%,[272] could also be influencing the increase in calcium oxalate stones. Obesity has also been recognized as a risk factor in the formation of calcium oxalate stones in human medicine.[6,273]

Indoor cats run a three-fold risk of developing urolithiasis with calcium oxalate stones compared with cats that are free to roam.[25,269]

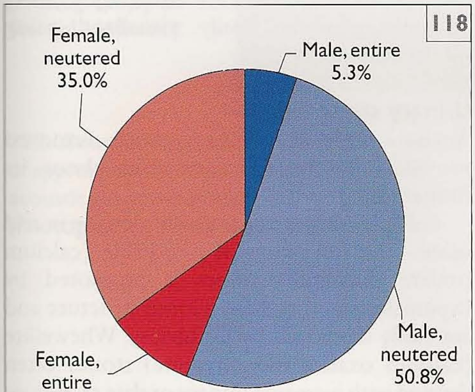
PATHOGENESIS

The increase in calcium oxalate urolithiasis in cats in the 1980s is frequently linked to changes in the cat population. However, Lekcharoensuk *et al.* (2000) were able to demonstrate that changes in breed frequency, age, gender, and reproductive status are not responsible for the increased prevalence of calcium oxalate and the decreased prevalence of struvite stones.[15] These factors could represent a risk for the formation of both kinds of stones.

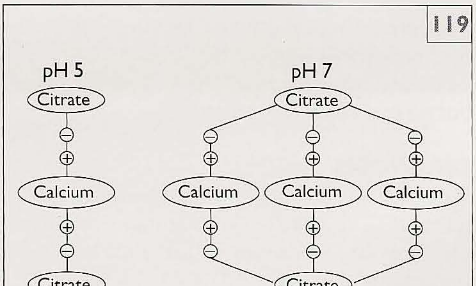
Table 41 Percentage frequency of calcium oxalate stones in cats in some European countries (1999–2001).[8]

Country (total stones)	Whewellite	Weddellite	Total
Switzerland (n = 91)	25.3	33.0	58.3
Netherlands (n = 199)	19.1	34.7	53.8
Germany (n = 749)	19.5	20.7	40.2
France (n = 51)	5.9	23.5	29.4
Finland (n = 53)	9.4	9.4	18.8
Austria (n = 41)	7.3	9.8	17.1
Italy (n = 81)	5.0	6.3	11.3

The increasing frequency of calcium oxalate stones in cats runs more or less parallel with the changes in food composition to aid urine acidification and prevent struvite stones. It has been proven that diets with a low sodium, potassium, protein, and moisture content increase the risk of calcium oxalate stone formation.[15] However, it is generally acknowledged, in both humans and dogs, that a high protein intake promotes acidosis and thus leads to hypercalciuria and hypocitraturia and increases the risk of calcium oxalate stone formation.[168,202,274] The statements on the prophylactic effect of protein in calcium oxalate stones can be explained by the observation that high protein intake in cats results in increased water intake and a larger volume of urine.[275] In addition, the administration of high levels of protein also increases potassium levels, which is often lacking in cats with calcium oxalate stones. The significance of protein intake in cats with calcium oxalate stones remains unresolved at this time. Experience suggests that normal intake should be allowed, but over-supply avoided. Lekcharoensuk *et al.* also state that low magnesium intake in cats is linked to an increased risk of calcium oxalate stone formation, whereas excessive intake increases the risk of struvite stones, so the aim should be a normal intake.[275] This also applies to phosphate, which binds calcium intestinally and thus prevents hypercalciuria. An excessive supply of phosphate, however, reduces the free calcium to a level insufficient to bind dietary oxalate with resulting hyperoxaluria. This in turn entails a very high risk of calcium oxalate stone formation.[169,170] This is plausible, because the molar ratio of calcium to oxalate in the urine is 10:1, whereas calcium oxalate binds 1:1, so urine always contains a marked excess of free calcium, which binds very easily to excess oxalate to form poorly soluble calcium oxalate. It is generally acknowledged that that urine-acidifying diets reduce the urinary excretion of citrate. In urine, citrate is the strongest inhibitor of calcium oxalate crystallization, as it binds with free calcium to a form a soluble complex. The citrate-binding capacity of calcium in the acid pH range is very small (**119**), therefore treatment should aim to adjust the urine pH to 6.2–6.8 to optimize the citrate–calcium bond. Higher pH values should be avoided, as they promote the formation of phosphate stones. A regular acidifying diet that achieves urine pH values of <6.2 and that has not been shown to promote urine dilution could promote calcium oxalate stone formation.[269] For an exact risk assessment further parameters have to be taken into account.[269]



118 Gender distribution of cats with calcium oxalate stones (total sample n = 1,797, calcium oxalate stones n = 468).[8]



119 Formation of the highly soluble calcium citrate complex with varying bonding capacity for calcium at different pH values.

The pathogenesis of calcium oxalate stone formation is complex, significant elements include dietary composition (electrolytes, oxalate), low urine volume (high specific gravity), and a very acidic urine pH.

Low urine volume is often crucial for stone formation in cats, and sodium chloride should be added to the diet to stimulate water intake. In cats and dogs raised blood pressure is not a risk with moderate sodium chloride administration (3.75 g/1000 kcal).[176,276] A dietary sodium content of 1.5% is therefore not considered to be a health risk.

As with dogs, the formation of calcium oxalate stones in cats is an exceptionally complex process (**120**). Breed predispositions, increasing age, neutering, low levels of activity (indoor cats), and inappropriate diets, e.g. with a strong acidifying effect or inadequate moisture content, are the main causes of increased potential for the formation of calcium oxalate crystals in urine, which can aggregate into microliths and stones if insufficient inhibitors are present. Macromolecular substances, such as glycosaminoglycan, Tamm-Horsfall proteins, nephrocalcin, and uropontin, can significantly inhibit the formation of microliths but also trigger it. The role played by macromolecular substances in stone formation is very complex and the subject of specialized research.[277]

In cats, up to 35% of all animals with calcium oxalate stones present with hypercalcaemia,[239] and primary hyperparathyroidism or an idiopathic hypercalcaemia must be considered.[278,279] Acidosis is being discussed theoretically as a cause, but no cases have been reported.

DIAGNOSIS

Calcium oxalate stones have a high rate of recurrence at 30%,[280] so an accurate diagnosis for the first occurrence of urolithiasis is important.

Urinalysis

- Specific gravity: mostly >1.035.
- pH: acidic, frequently <6.2.
- Calcium oxalate stones can lead to secondary bacterial urinary tract infections, so a culture should always be prepared from urine obtained by a sterile technique.
- The dipstick may show signs of cystitis (protein, haemoglobin/blood).
- Crystalline urine sediment: envelope- and dumbbell-shaped crystals (**29**) (not definite proof of calcium oxalate stones!). Fewer than 50% of cats with calcium oxalate stones present with crystalluria at the time of diagnosis.[281]
- Quantitative urinalysis is required to determine the RSS of urine with calcium oxalate (fractional electrolyte excretion).
- RSS with calcium oxalate as a measure of the risk of stone formation can be calculated with the EQUIL or SUPERSAT computer programs.[94,95]

Blood tests

Renal parameters are within the reference range, unless calcium oxalate stones are present bilaterally in both kidneys with consequent stasis and renal failure or in the event of an obstruction.

Hypercalcaemia can cause calcium oxalate stones, therefore calcium or, ideally, ionized calcium should always be measured.[278,282] In the event of hypercalcaemia all possible causes (in particular primary hyperparathyroidism) must be investigated.[279]

Acid–base parameters are usually within the reference range, except in the event of an obstruction.

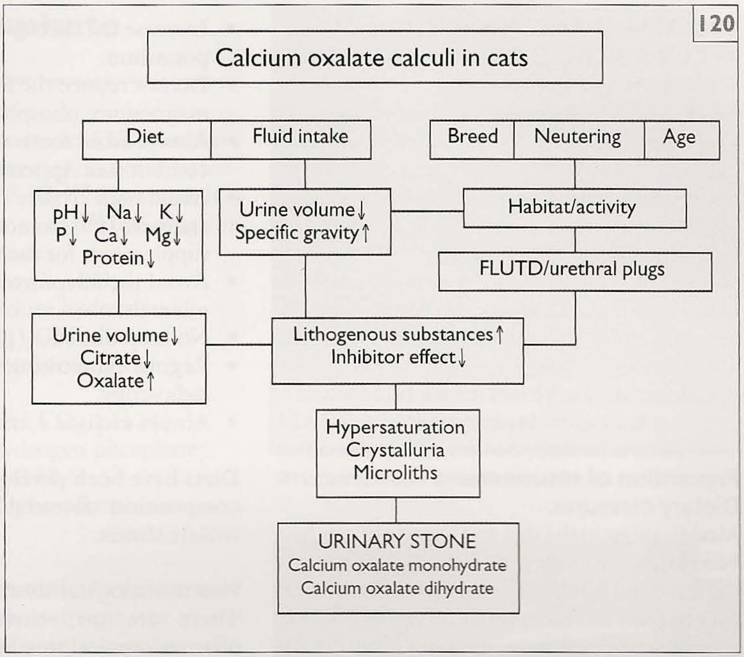
Diagnostic imaging

Calcium oxalate stones are radiopaque (**121**) and can also be easily visualized using ultrasonography (**122**).

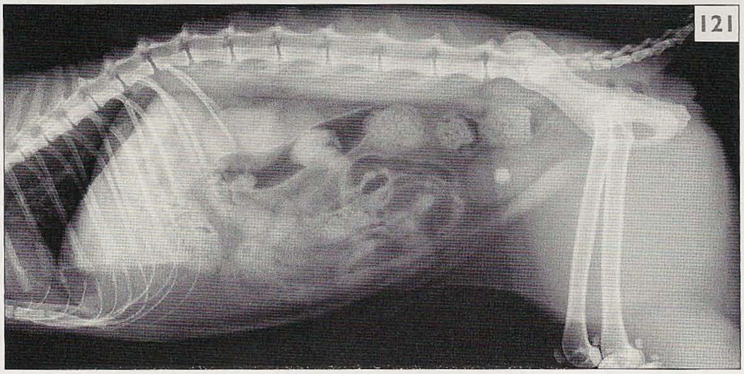
Urinary stone analysis

Analysis of every urinary stone removed provides important information about its formation.

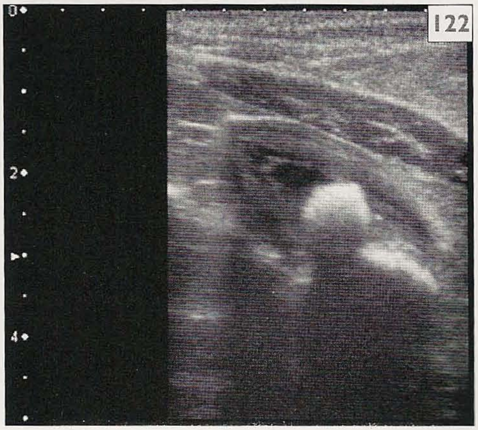
Calcium oxalate stones usually develop in acid urine. The formation of weddellite (calcium oxalate dihydrate) stones is promoted by hypercalciuria, they have a loose structure and are easily destroyed by lithotripsy. Whewellite (calcium oxalate monohydrate) stones often develop with increased urinary oxalate excretion; they are very solid and compact. If struvite is also detected, it is probable that an infection or very high urine pH combined with low urine production were involved in the development of the stone. See Chapter 1.


120
Calcium oxalate calculi in cats
Diet
Fluid intake
Breed
Neutering
Age
pH↓ Na↓ K↓
P↓ Ca↓ Mg↓
Protein↓
Urine volume↓
Specific gravity↑
Habitat/activity
FLUTD/urethral plugs
Urine volume↓
Citrate↓
Oxalate↑
Lithogenous substances↑
Inhibitor effect↓
Hypersaturation
Crystalluria
Microliths
URINARY STONE
Calcium oxalate monohydrate
Calcium oxalate dihydrate

120 Diagram of the pathogenesis of calcium oxalate stone formation in cats.



121 Irregular bladder stone in a female, neutered 4-year-old Shorthair. The stone was surgically removed and was composed of 100% calcium oxalate dihydrate (weddelite). (Photograph by Dr C. Stengel, Hofheim.)



122 Ultrasound scan of the cat in **121**. A stone of approximately 6 mm diameter with distal acoustic shadow is present in the bladder. (Photograph by Dr C. Stengel, Hofheim.)

TREATMENT AND PREVENTION OF RECURRENCE

Treatment

Small symptomatic stones can be removed by urohydropropulsion or aspirated through a catheter; otherwise, surgical removal will be necessary. A renal transplant can be considered for cats with chronic renal failure caused by calcium oxalate stones – in a sample of 19 cats the average survival time after transplant was >600 days.[282] In five cats, stones also developed in the allograft, while two of them had hypercalcaemia.

> Calcium oxalate stones cannot be dissolved *in vivo*.

Prevention of recurrence

Dietary measures

Modifications in the diet and lifestyle of cats have been identified as the main factor responsible for the increased incidence of calcium oxalate stones over the past 25 years; dietary measures therefore play a significant role in the prevention of recurrence. As described in the section on pathogenesis, there is much controversy over the role of protein intake. However, as cats are inherent carnivores and are dependent on an adequate supply of protein, protein intake should not be restricted. The following general recommendations can be made:

- Promote diuresis: clean water *ad libitum*, add water to food. Aim for a specific gravity of <1.030.
- Use nondry food if possible, otherwise feed moistened dry food or a special prophylactic diet.
- Provide optimal conditions to encourage regular urination, clean cat litter (n+1 for households with several cats).
- Increase physical activity.
- Avoid excess weight.
- Do not feed *ad libitum*.
- Avoid stress factors.
- While the solubility of calcium oxalate is barely influenced by urine pH, it has been shown that the discontinuation of an acidifying diet can normalize serum calcium.[283] Acidifying diets which have not been tested to assess their effects on urine composition or pure acidifying diets or the addition of urine-acidifying drug should be avoided. Adjust the urine pH to 6.5–6.8.[284]
- Increase the dietary intake of sodium and potassium.
- Do not reduce the intake of calcium, magnesium, phosphate, and dietary fibre.
- Always avoid foods with high oxalate content (see Appendix, p. 145).
- Avoid high-oxalate supplements with cranberry.[285] Do not provide vitamin C supplements for the same reason.[284]
- Avoid the uncontrolled administration of minerals.
- No loop diuretics (furosemide).
- Regular monitoring with ultrasound or radioscopy.
- Always exclude a urinary tract infection.

Diets have been developed that modify urine composition favourably to avoid calcium oxalate stones.

Pharmacological treatment

There are no reliable studies into the pharmacological treatment of calcium oxalate urolithiasis in cats. In problematic cases, the only reference possible is from experiences in human medicine or dogs (see Chapter 2). Drugs should only be used after specific blood tests and urinalysis.

The formation of calcium oxalate stones is more or less pH-independent. Alkalinization with potassium citrate (50 mg/kg orally q12h) should only be attempted for *permanently* acidic urine (pH <6.0). The dosage must be titrated to the desired pH value (6.2–6.5) by conducting frequent checks.

Hydrochlorothiazide could be tried to reduce calcium excretion in cases of proven hypercalciuria. Its efficacy and the incidence of adverse reactions have yet to be studied.

Calcium phosphate stones

INTRODUCTION

Pure calcium phosphate stones (**123**) are very rare in cats and many studies do not differentiate them further.[26,259,261,268] However, it is possible to make an analytical distinction between various phosphates:

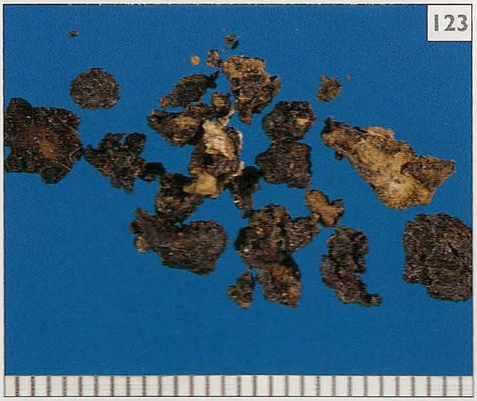
- Tricalcium phosphate $Ca_3(PO_4)_2$.
- Hydroxyapatite (calcium hydroxyl phosphate) $Ca_5(PO_4)_3OH$.
- Carbonate apatite (carbonate-rich hydroxyapatite) $Ca_{10}(PO_4,CO_3)_6(OH,CO_3)_2$ (**124**).
- Brushite (calcium hydrogen phosphate dihydrate) $CaHPO_4{\cdot}2\,H_2O$.
- Amorphous calcium phosphate.

EPIDEMIOLOGY

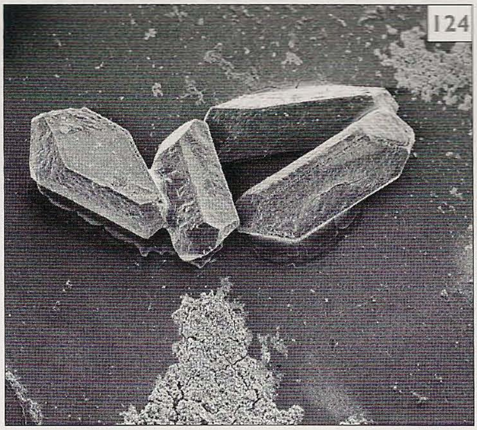
A European study observed carbonate apatite and brushite stones most frequently in the European Shorthair. These stones are also occasionally found in Persians, Chartreux, and Siamese. Male animals were affected more frequently with carbonate apatite stones (male:female ratio 2.9:1), whereas females showed a slightly higher predisposition for brushite stones (male:female ratio 1:1.2). More than 80% of cats with the aforementioned stones were neutered.[8] The recurrence rate was 20–27%, and 45–50% of cats with calcium phosphate stones were obese. See *Table 42*.

PATHOGENESIS

The analytical differentiation of the various calcium phosphates does not provide any conclusions regarding their respective pathogenesis in cats. Experience from human medicine, however, shows that phosphates should be differentiated between trivalent phosphate ions (PO_4^{3-}), which crystallize with calcium ions in an alkaline milieu, and divalent (acid) phosphate ions (HPO_4^{2-}), such as those found in brushite. Calcium phosphates from alkaline urine are commonly grouped under the generic term *carbonate apatite* (*Table 42*). This is because the crystallization conditions in the urine cause carbonate ions to be embedded in the crystal lattice, where they can be detected by infrared spectrometric analysis.[110] Brushite has been identified as an acid phosphate in urinary stones in cats (*Table 42*). Amorphous calcium



123 Calcium phosphate stones in a cat, carbonate apatite, microcrystalline, crumbly structure, black–brown crystals.



124 Crystals in urine sediment: large struvite crystals and pseudoamorphous carbonate apatite, scanning electron microscope image.

Table 42 Frequency of different calcium phosphates in urinary stones in cats.
*These phosphates can be classified together as carbonate apatite.[8,16,27,78]

Stone type	Europe% (n = 1,797)	USA% (n = 9,481)
Calcium phosphate*	2.1	0.6
Tricalcium phosphate*	0.4	<0.1
Amorphous calcium phosphate	0.3	-
Brushite	0.7	0.2

phosphate consists of such fine particles that the analytical method described – x-ray diffraction – is unable to detect a crystalline structure; infrared spectrometry is required for their analysis. Amorphous calcium phosphate is formed in urine with marked supersaturation with calcium and phosphate ions and fast crystallization.

Crystallization of all calcium phosphates is determined by the pH value, as they are poorly soluble above pH 6.8. Postprandial rises in pH and high concentrations of calcium and phosphates in urine can promote the formation of calcium phosphate stones (carbonate apatite) even without a urinary tract infection.

Brushite stones occur in acid urine with pH 6.5–6.8. However, they also require a very high concentration of calcium in the urine, such that concomitant diseases, e.g. primary hyperparathyroidism, should be investigated where these stones are present. Brushite urinary stones have a high rate of recurrence.

DIAGNOSIS AND TREATMENT

So far, there is no specific diagnosis and treatment for the different calcium phosphate stones in cats. Reference should therefore be made to the treatment of these types of stone in dogs (see Chapter 2).

Comprehensive metabolic tests should be conducted if stone formation recurs.

Urate stones

INTRODUCTION

Urates, at 3–6%, are the third most common type of stone in cats, after struvite and calcium oxalates. In more than 90% of cases, urate stones are composed of ammonium urate (**125, 126**); so far only isolated cases with sodium and potassium urate have been described. Based on the current state of knowledge, all these cases are subsumed under the collective term urate urolithiasis.

EPIDEMIOLOGY

Larger studies have observed varying frequencies of urate stones in cats (*Table 43*).

A purely genetic variant of urate urolithiasis, as found in the Dalmatian, has not been verified in cats. A European study recorded that 79% of urate stones occurred in European Shorthairs, 10% in Persians, and 5% in Siameses.[8] Sixty-five percent were male animals and in more than 90% of cases, the cats were neutered. The high proportion of obese animals (>65%) among cats with urate stones was particularly noticeable.

PATHOGENESIS

Little information is available about the aetiology of urate stone formation in cats. The high proportion of obesity indicates that overfeeding and increased purine intake with offal and other meat products may play a role. Urate stones form mainly in alkaline urine, so a permanently high pH value (>7.0) with urate excretion and low urine volume can promote the formation of stones. A portosystemic shunt or other hepatic diseases can also be associated with urate stones (Dr M. Schneider, Gießen, personal communication).

DIAGNOSIS

Urine analysis

- Specific gravity: mostly >1.030.
- pH: always >7.0.
- Characteristic crystals in urine (**29**).
- Quantitative measurement of uric acid.

Blood tests

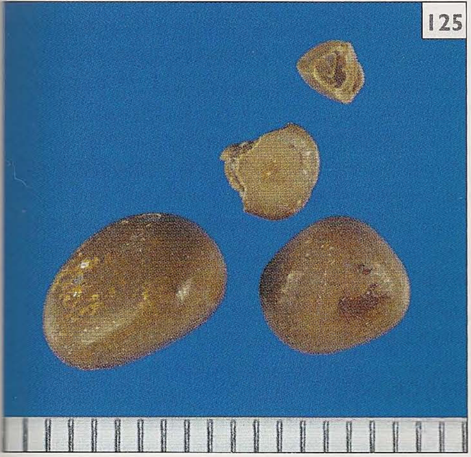
If a hepatic shunt is present, the serum urea value can lie below the reference range. In the event of urate stones a bile acid stimulation test should always be performed to rule out portosystemic shunts.[286] Serum uric acid is seldom measured, but can be elevated. Except in the event of an obstruction and concomitant problems with urine flow, renal parameters are within the reference range.

Diagnostic imaging

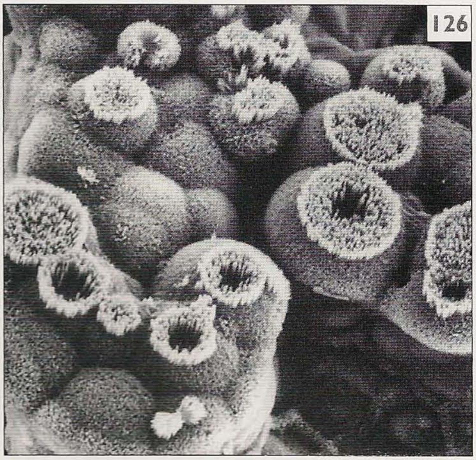
- Urate stones cannot usually be detected by radiography (**127**).
- Reliable evidence can usually be obtained with ultrasound but urate stones are often very small and easily overlooked (**128**).

Urinary stone analysis

Urinary stone analysis with infrared spectrometry will confirm the diagnosis. See Chapter 1, p. 30.

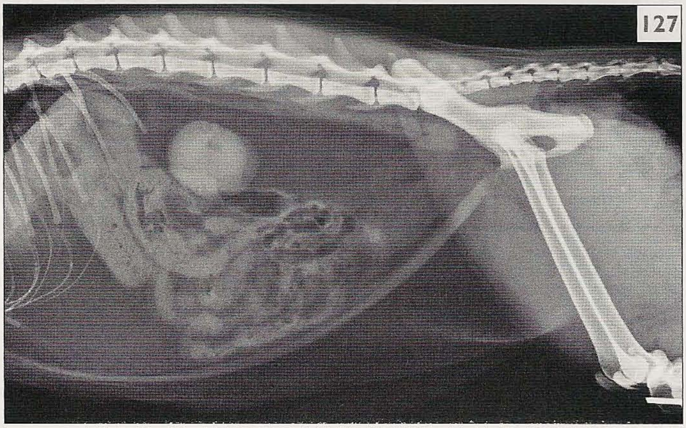


125 Ammonium urate stones in a cat, smooth surface, firm structure.



126 Ammonium urate crystals, crystals grouped in a sphere, scanning electron microscope image.

127 Abdominal radiograph of a 3-year-old, male, neutered European Shorthair cat, with several bladder stones visible with ultrasonography (see **128**). (Photograph by Dr C. Stengel, Hofheim.)



128 Ultrasound scan of the bladder of the cat in **127**. One large and several smaller stones and urinary gravel were present. The stones were surgically removed and analysis showed them to be 100% urate. (Photograph by Dr C. Stengel, Hofheim)

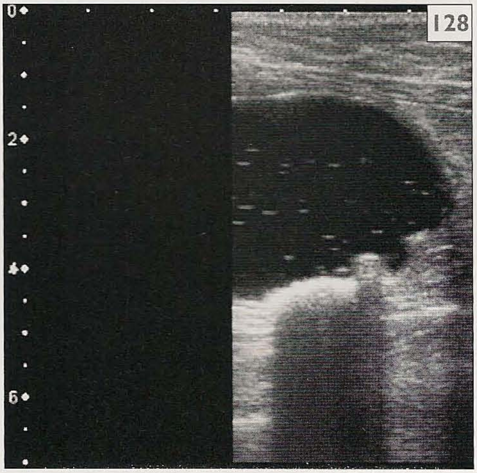


Table 43 Frequency of urate stones in cats in different regions.[16,26,27,78,259]

Region	**Urate stones (%)**
Europe (n = 1,797)	3.2
USA (n = 9,481)	6.1
Canada (n = 4,730)	3.1

TREATMENT AND PREVENTION OF RECURRENCE

Treatment

Stones may be removed by spontaneous voiding, urethral massage, urohydropropulsion, or by surgery for large symptomatic stones.

There is no confirmed data on dissolving stones, but in selected cases, this may be attempted using an appropriate diet and medications, as with dogs (see Chapter 2).

Prevention of recurrence

Once all of the stones have been removed or dissolved, general prophylactic measures, e.g. urine dilution, should be consistently applied. When changing to a new diet, low-purine foods (see Appendix, p. 147) should be included. If high levels of uric acid are detected in the serum or urine, the recommended treatment is the administration of allopurinol for a limited period of time (10–20 mg/kg/24h), while conducting regular checks.

Cystine stones

INTRODUCTION

As in other species, cystine stones in cats are mostly of a yellowish colour with a greasy, shiny surface. Cases frequently present with many small concretions (**129**) in the bladder, which can become stuck in the urethra in male animals.

EPIDEMIOLOGY

Cystine stones are rare in cats and represent only 0.3–0.6% of all urinary stones.[16,27,78] The first reported case of cystine urolithiasis in cats was in a wildcat.[287] Some breeds have shown a predisposition for the formation of cystine stones; a European study diagnosed 6 of 11 stones in Siamese, three in European Shorthair cats, and two in other breeds. It is also remarkable that nine of the cats with cystine stones were female and seven of those were neutered. The recurrence rate of 45% was the highest of all types of stone.[8]

> Cystine stones have the highest recurrence rate of all urinary stones in cats.

PATHOGENESIS

A genetic defect which affects the renal reabsorption of dibasic amino acids is responsible for cystinuria. This results in the excessive excretion of various amino acids with the urine; of these only cystine is poorly soluble at a physiological urine pH thus causing urolithiasis.

A case report of a Siamese cat with cystine stones reported a high urinary specific gravity of 1.047 and acidic urine with a pH of 5.5.[288] This indicates that permanently acidic urine promotes cystine urolithiasis in affected cats, in addition to the genetic defect. The solubility of cystine is heavily pH-dependent and only begins to increase with a urine pH >7.5.

DIAGNOSIS

Urinaysis

- Specific gravity: >1.035.
- pH: <6.2.
- Crystalline urine sediment – pathognomonic hexagonal crystals (**29h, 130**).

Blood tests

Renal parameters are within the reference range, except when cystine stones cause a urinary obstruction.

Diagnostic imaging

Cystine stones are weakly radiopaque, so an additional ultrasound scan or double-contrast radiographic examination should be performed in the event of cystinuria.

Urinary stone analysis

Stone analysis using the recognized methods of infrared spectrometry or x-ray diffraction can be used to verify the genetic defect. See Chapter 1.

TREATMENT AND PREVENTION OF RECURRENCE

Treatment

Cystine stones can be dissolved using diet and drugs. Symptomatic stones (causing an obstruction) must be removed by urohydropropulsion or surgery. For treatment options, refer to Chapter 2 on dogs (p. 91).

Prevention of recurrence

The genetic defect requires life-long prophylaxis. The necessary measures are described in detail in Chapter 2 on cystinuria in dogs (p. 91). In the rare cases of cystinuria in cats, an appropriately adapted treatment plan should be applied.

If cystinuria is diagnosed in breeding animals, then the entire breeding family should be investigated and cystinuric animals excluded from further breeding.

Xanthine stones

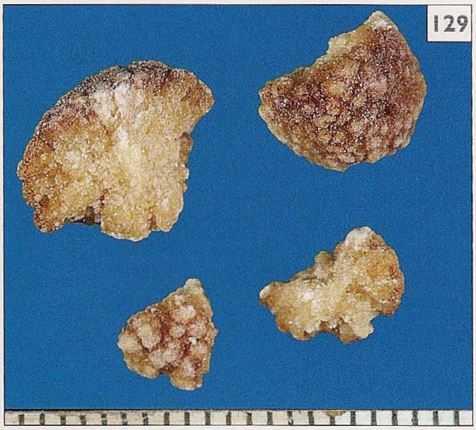
INTRODUCTION

Urolithiasis with xanthine stones is a very rare disease in cats. The stones are usually small, spherical and yellow/brown in colour (**131**, **132**). In the few reported cases they were found in high numbers (n = 30–40). As a rule, a reliable diagnosis can only be obtained by analysing the stones after removal.

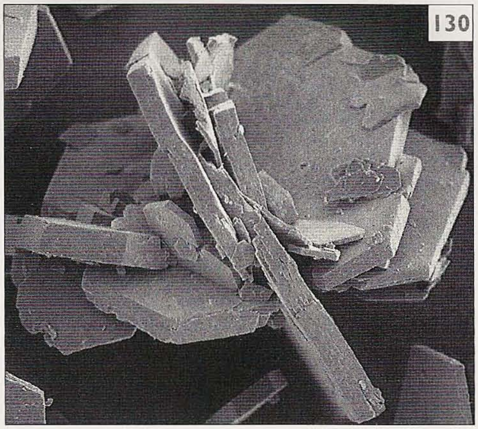
EPIDEMIOLOGY

Only a few, mostly insufficiently documented case descriptions exist, e.g. that of a 5-year-old neutered male Shorthair with intermittent dysuria.[290] A single case of xanthine urolithiasis was reported in a 1985 study of 41 urinary stones from cats.[259] Only a few xanthine stones are described in comprehensive research conducted by stone analysis centres:

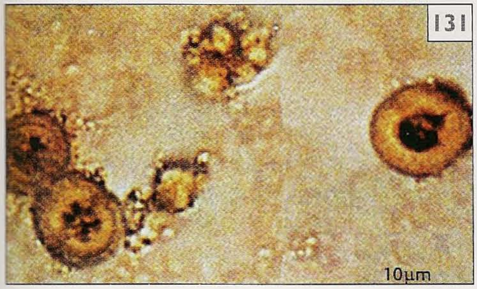
- USA (9,481 urinary stones): 11 cats with xanthine stones.[27]
- Europe (1,797 urinary stones): 6 cats with xanthine stones.[8]



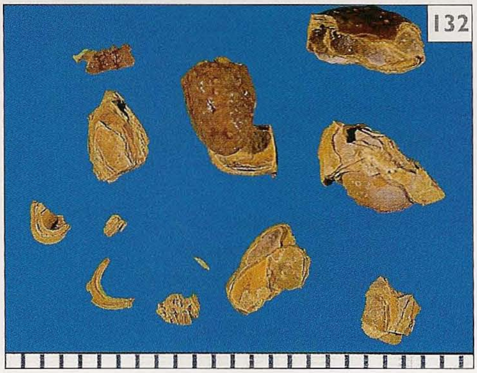
129 Cystine stone from a cat, microcrystalline structure, mulberry-shaped surface.



130 Cystine microlith in urine sediment, typical hexagonal crystals, scanning electron microscope image.



131 Xanthine crystals in urine sediment.[289]



132 Broken pieces of xanthine stone.

PATHOGENESIS

As with xanthine urolithiasis in dogs (see Chapter 2), there are two possible causes of increased xanthine excretion in urine: the first is a genetic defect in the formation of xanthinoxidase, and the second is the inhibition of xanthinoxidase by allopurinol used in the treatment of urate urolithiasis.

Both situations may be seen in cats. It is therefore important to check for a history of allopurinol treatment, even if it has been discontinued for some time.

DIAGNOSIS AND TREATMENT

There are no specific data available about the treatment of xanthine urolithiasis in cats. It is therefore advisable to apply the same principles as those used in dogs (see Chapter 2, p. 97). Additionally, in the event of a confirmed diagnosis of xanthine urolithiasis, a metabolic examination with quantitative xanthine urinalysis is recommended[291] to expand our knowledge of this disease in cats.

If genetic xanthinuria is diagnosed in breeding animals, then the entire breeding family should be investigated and affected animals excluded from further breeding.

Silicate stones

Silicate stones do not occur in cats; in studies from large analysis centres[27] they are occasionally mentioned with no figures quoted[26] or reported as individual cases (n = 4)[8]. As yet, there are no published clinical case reports of silicate urolithiasis, so it is impossible to prove whether the cases reported by the laboratories are of silicate stones that have formed *in vivo*, as described for dogs (see Chapter 2, p. 100) or whether artefacts, e.g. from the cat's litter, were the object of analysis. Therefore, any analysis that indicates the presence of silicate stones should first be investigated to exclude artefacts.

Causes for the true formation of silicate stones could include:

- Food containing silicate.
- Food contaminated with sand.
- Pica (abnormal appetite, intake of urine, earth, stones).
- Drugs containing silicate.

A confirmed diagnosis requires thorough investigation. The prevention of recurrence is the same as that described for dogs.

Drug-induced urinary stones

The formation of urinary stones from drugs has not been reported in large analytical stone studies in cats.[8,26,27,78] The possible formation of stones from sulfadiazine and sulphonamides and their metabolites has been described.[14] Small quantities of drug metabolites can occasionally be detected in calcium oxalate and struvite stones (Prof. A. Hesse, Bonn, personal communication).

Overall, drug-induced urinary stones are of no significance in cats. If they should be diagnosed, successful prophylaxis can be achieved by discontinuing or changing the medication.

Potassium magnesium pyrophosphate

Potassium magnesium pyrophosphate urinary stones were initially described in four Persian cats,[292] and subsequently in ten more cats (two Himalayan, two Persian, one Maine Coon, five Shorthair).[293] A core of calcium oxalate (n = 8) or struvite (n = 1) surrounded by pyrophosphate stones was found in nine further cats.[293] A link with a temporary or persistent enzymatic dysfunction is suspected, which causes the formation of crystals and the development of potassium magnesium pyrophosphate stones, due to the supersaturation of urine with pyrophosphate.[292]

Matrix, matrix stones, blood clots

When crystals are formed in urine, organic macromolecular substances, which are physiologically excreted via the kidneys in varying concentrations, are embedded in the crystals or deposited on them. Macromolecular compounds in urinary stones are called matrix substances, they mostly consist of Tamm-Horsfall glycoprotein, uromucoid, glycosaminoglycans, nephrocalcin, albumin or other macromolecular proteins.[277,294,295]

In vitro experiments have proved that Tamm-Horsfall glycoprotein in cat urine increases the crystallization of struvite, whereas albumin has no effect. Tamm-Horsfall glycoprotein has both a promoting and inhibiting effect on the crystallization of calcium oxalate and calcium phosphate.[296,297] Significantly higher concentrations of Tamm-Horsfall glycoprotein were found in the urine of male cats with stones compared to that of healthy animals.[298]

Organic material in urinary stones does not necessarily have to have been secreted by the kidneys, but can also be produced by the epithelial cells of the urinary tract following trauma or other pathological changes. Dead cells and bacteria can also act as seed crystals. The excretion of matrix substances can also be caused by bacterial or viral infections. The formation of urethral plugs and protein stones must be ascribed to such processes.[299,300]

Extraneous causes, infections, tumours, or urolithiasis can cause internal bleeding, which leads to blood clots that become adherent and solidify over time. They can develop into hard, stone-like bodies that do not contain any crystalline material and are radiolucent. A study of stones in cats, describes these formations as dried, solidified blood calculi.[301] The concretions (n = 49) were removed surgically or at post mortem and the assumption is that they had already solidified to this extent *in vivo*. Precise analytical examinations determined a blood-like composition in the majority of these stones. Only a few samples contained small quantities of calcium oxalate monohydrate or calcium phosphate crystalline material.

Infrared spectrometry has helped to analyse all noncrystalline stones as organic protein-rich samples.

The removal of matrix or blood stones should always be followed by further diagnostic clarification.

Macromolecular organic substances (matrix) in the urine can affect the development of stones as follows:

- Facilitate the nucleation of crystals.
- Organize crystal growth.
- Act as a filler between the crystals.
- Form larger organic masses that fill cavities in the urinary system (matrix stones).
- Passive behaviour in the crystallization of mineral substances (albumin).
- Inhibit crystal aggregation.

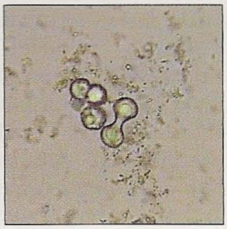
Hospital Veterinário de Trás-os-Montes

CHAPTER 4

Urinary stones in rabbits and guinea pigs

Urinary stones in rabbits

Urinary stones in guinea pigs



Urinary stones in rabbits

There are very few published reports of urinary stones in rabbits, but the increasing popularity of these animals as pets has made them a common sight in small animal practice.

Most stones are yellowish to brown in colour and can also be almost white. They usually present as multiple bladder stones, but large solitary stones can also develop (**133**, **134**).

EPIDEMIOLOGY

For a long time, publications on urinary stones in rabbits were limited to the description of individual cases.[19-21,146,153] Crystalline material in urine sediment was described very early on and identified as calcium carbonate.[302] The primary component in the majority of urinary stones in rabbits was identified as calcium carbonate (calcite),[200] which concurs with the statement that this is the most common stone type in herbivorous mammals.[303] A detailed report of nine clinical cases clearly describes the wide range of clincial signs and stone types that can be found in rabbits.[304]

In a series of 35 urinary stones in rabbits, the average age of the animals was 3.7 years (range: 1–8 years). Male animals were affected slightly more often (male:female ratio 1.2:1). Sixteen percent of the animals with stones were classified as obese and 12% had already suffered from recurrence of the disease. More than 90% of the stones were surgically removed from the lower urinary tract (bladder, urethra).[305]

The composition of urinary stones in rabbits was established in a large series (n = 269) (*Table 44*).[8] Calcium carbonate (calcite) was identified as the main component in >90% of cases. Calcium phosphate is primarily found as very fine deposits (pseudoamorphous to amorphous). Calcium oxalate or struvite were rarely found and only as mixing components in other urinary stones.

PATHOGENESIS

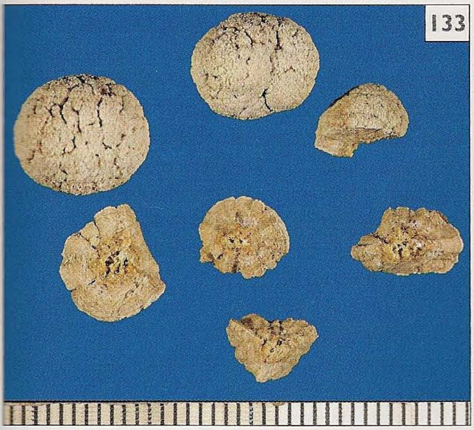
The diet and metabolism of herbivores result in an alkaline urinary pH of between 7.5 and 9.5. These conditions favour the crystallization of phosphates and carbonates as soon as sufficient concentrations of these anions and corresponding concentrations of cations (calcium, magnesium) are present in the urine (**135**). Experimental studies in rabbits have shown that a high dietary calcium intake does not reduce the intestinal absorption of calcium, instead the calcium balance is regulated by increasing the renal excretion of calcium.[306] These studies measured calcium concentrations up to 18 g/l with calcium-rich foods and with no increase in urine volume. This led to the conclusion that adult rabbit food should contain 5 g/kg, which should be increased to a maximum of 8 g/kg calcium during growth and lactation. These studies also provide a possible explanation for the high calcium excretions seen in association with urolithiasis.

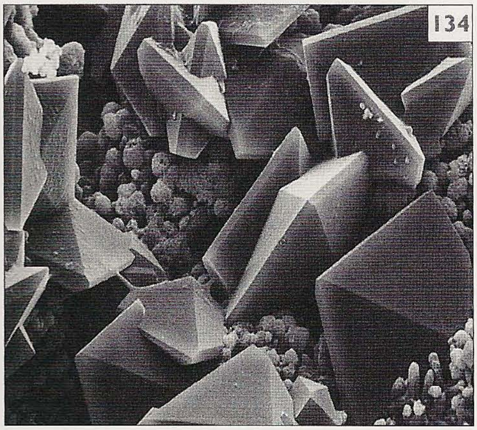
The specific gravity of urine in rabbits with urolithiasis is relatively low at 1.012.[21]

A high pH value and a high urinary calcium concentration are crucial for calcium carbonate crystallization in urine. Urinary stone analysis with infrared spectrometry has shown that the calcium carbonate components of urinary stones in rabbits crystallize with the mineralogical crystal structure of calcite.[110,305] *Aragonite*, another crystal structure of calcium carbonate, has yet to be detected in urinary stones in rabbits, whereas *vaterite* has only been found in a few cases.[304]

Insufficient dietary phosphate intake promotes the intestinal absorption of calcium, because less calcium can be bound in the intestine as poorly soluble calcium phosphate. However, if excess phosphate is administered, calcium phosphate crystals can form rapidly and become embedded in growing urinary stones.[38] Pure calcium phosphate stones are very rare in rabbits (*Table 44*).

If calcium oxalate is detected during urinary stone analysis in rabbits, this can be attributed to a high oxalate diet (see Appendix, p. 145). An unbalanced diet of oxalate-rich plants with insufficient calcium intake can lead to very high concentrations of oxalate in the urine, which can crystallize out as calcium oxalate and become embedded in a urinary stone.





133 Bladder stones in a rabbit; 80% calcite and 20% amorphous calcium phosphate.

134 Scanning electron microscope image of a bladder stone in a rabbit (cut surface); 55% calcite, 35% weddellite, 10% amorphous calcium phosphate; large bizarre individual crystals (weddellite) and pseudoamorphous spherical aggregates (calcium phosphate).

135 Diagram of the pathogenesis of urinary stones in herbivores.

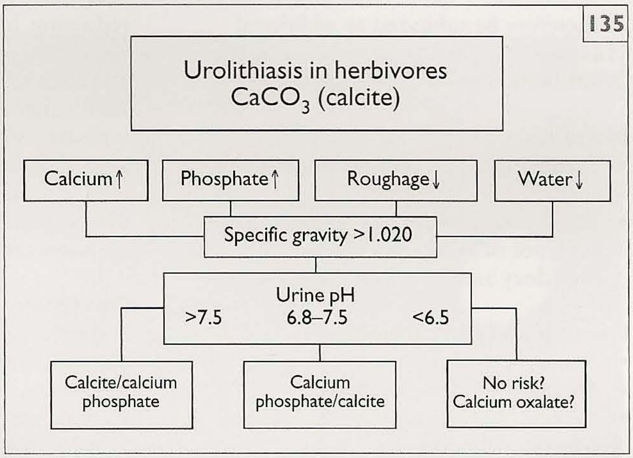

135
Urolithiasis in herbivores
$CaCO_3$ (calcite)
Calcium↑
Phosphate↑
Roughage↓
Water↓
Specific gravity >1.020
Urine pH
>7.5
6.8–7.5
<6.5
Calcite/calcium phosphate
Calcium phosphate/calcite
No risk? Calcium oxalate?

Table 44 Analysis of urinary stones in rabbits using infrared spectrometry (n = 269).[8]

Result	**Female %**	**Male %**	**Unknown %**	**Total %**
Primary/secondary component	n = 106	n = 142	n = 21	n = 269
Calcium carbonate/calcium phosphate (n = 216) (amorphous)	32.5	41.7	6.1	80.5
Calcium carbonate/calcium phosphate (n = 19) (crystalline)	3.1	3.4	0.4	7.2
Calcium carbonate (n = 11)	1.1	2.6	0.4	4.1
Calcium oxalate/calcium phosphate (n = 11)	0.7	2.6	0.7	4.0
Calcium phosphate (n = 7)	1.1	1.5		2.6
Calcium carbonate/calcium phosphate/struvite (n = 2)	0.4	0.4		0.8
Calcium carbonate/calcium oxalate/struvite (n = 1)		0.4		0.4
Calcium carbonate/calcium oxalate (n = 1)	0.4			0.4
Total	**39.6**	**52.6**	**7.8**	**100**

DIAGNOSIS

Urinalysis

- Specific gravity: 1.010–1.040.
- pH: mostly >7.5.
- Colourless to grey crystals are noticeable in crystalline urine sediment in the presence of calcite stones (**136**).
- Rabbits are frequently presented for haematuria which can be confirmed by urinalysis: haematuria, occasionally leucocytes, crystalluria, occasionally transitional epithelial cells in surface and deeper layers.
- There is a risk of the development of secondary urinary infections following urolithiasis; a sterile urine sample should therefore be subjected to additional bacteriological examination including antibiotic sensitivity testing.

Blood tests

- Serum calcium is only elevated in rare cases.
- Renal parameters are only raised in the presence of bilateral nephropathy caused by kidney and/or ureteral stones.

Imaging and clinical signs

- Anorexia, apathy.
- Bloated abdomen, bent back.
- Pain on bladder palpation, stones can often be palpated.
- Haematuria, perianal inflammation.
- Pollakiuria, micturition disorders.
- Preputial oedema with urethral stone.
- Meteorism, diarrhoea.
- Urinary and faecal tenesmus.

Urinary stones in rabbits are nearly always radiopaque and can be detected easily on plain radiographs (**137, 138**). Ultrasonography is obviously also suitable.

Urinary stone analysis

Care should be taken to use infrared spectrometry for the laboratory analysis of urinary stones in rabbits. Other methods, e.g. x-ray diffraction, cannot detect noncrystalline components (amorphous calcium phosphate). If possible, all of the stone material should be sent in for analysis. See Chapter 1, p. 30.

TREATMENT AND PREVENTION OF RECURRENCE

Treatment

In the cases described so far, all stones in rabbits were either removed instrumentally or surgically, and in a few rare cases they were spontaneously voided from the lower urinary tract. If the urethra is obstructed with stone material, quick action is required to ensure the animal's survival.

The surgical procedure for the removal of symptomatic urinary stones is the same as that used in dogs and cats. Urohydropropulsion can be used in female animals.

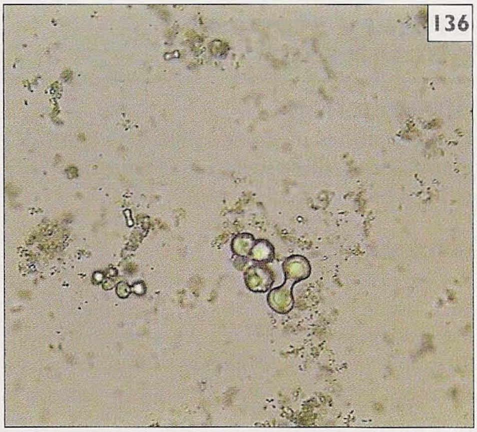
In the presence of gravel and definite analytical proof of calcium carbonate, a reduction in the formation of gravel may be achieved by administering acidifying foods, and, where appropriate, with the addition of acidifying drugs (L-methionine). Calcium carbonate stones would be expected to dissolve after reducing the pH to <6.5. However, no field reports are available for this treatment. The acidifying treatment should only be used in the short term.

Prevention of recurrence

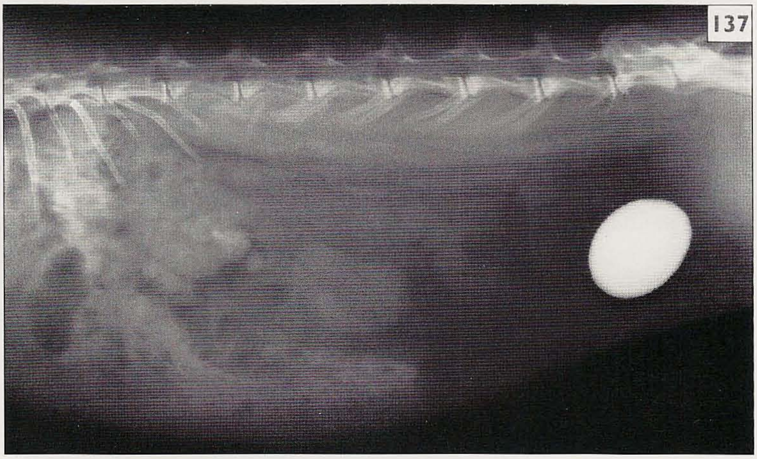
Preventive measures should be continued for a considerable period after stone removal. This involves:

- Appropriate mineral supply, especially calcium and phosphate.
- Appropriate vitamin supply (vitamin D 500–750 IU/kg food); the vitamin D content in commercial foods is often too high.
- Use of wet and green foods, e.g. carrots, salad.
- Avoid hay with a high proportion of lucerne (high calcium content), do not supply calcium licks, and do not feed dry foods.
- Increase fluid intake by offering table salt (1.5–7 g/kg food).
- Regular ultrasound monitoring during the first few months after stone removal.

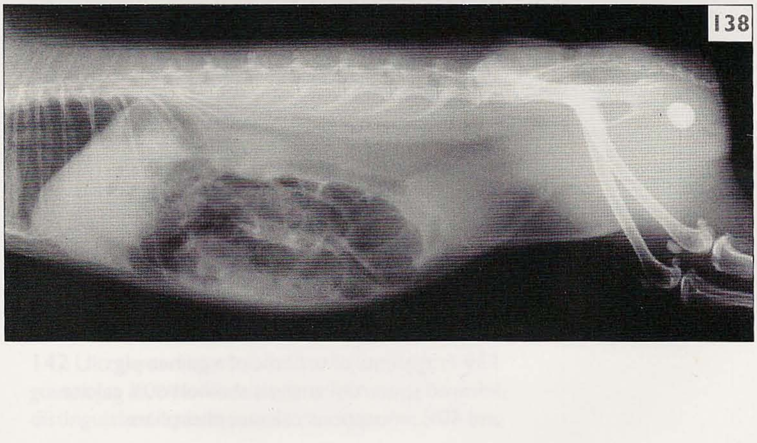
136 Crystalline urine sediment from a rabbit (pH 8.0), colourless to grey, small crystals next to individual spherical and dumbbell shapes, which dissolve with aerosis (carbon dioxide) on the addition of acetic or hydrochloric acid (differentiation from dumbbell shape in calcium oxalate monohydrate). (Photograph by M. Weber, Kleintierklinik (small animal clinic) Hüttig, Reutlingen).



137 Survey radiograph of a 3-year-old rabbit with haematuria and a large bladder stone.



138 Single calcium carbonate stone in the urethra of a male rabbit (age unknown).



Urinary stones in guinea pigs

INTRODUCTION

Urinary stones in guinea pigs have a rough, granular crystalline surface and are white–grey to light brown in colour (**139, 140**).

EPIDEMIOLOGY

Reports of urolithiasis in guinea pigs are rare and usually limited to the description of individual cases.[200,307-311] A series comprising 20 guinea pigs with urolithiasis describes female animals as being predominantly affected (female:male ratio 3:1).[22] The average age was 4.6 years (range: 2–8 years). In the male guinea pigs, all of the stones were located in the bladder. Female animals, on the other hand, were mostly affected by urethral stones (n = 13), which could be removed instrumentally or by palpation.

In the female guinea pig, the *ostium urethrae externum* opens out cranioventrally to the vaginal opening and is usually covered by the *praeputium clitoridis*. Urethral stones can cause swelling at the urethral orifice. All other stones were removed by cystotomy or urethrotomy.

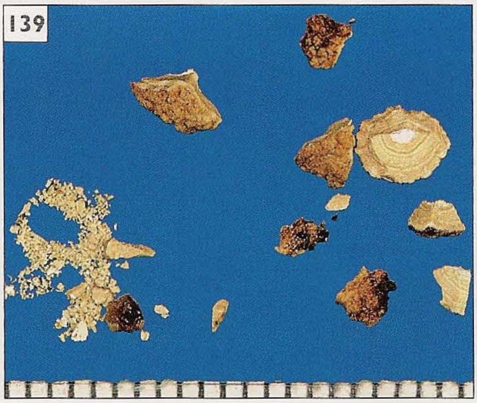
In the study quoted, 18 stones showed a high content of calcium carbonate, 12 stones also contained varying quantities (5–80%) of calcium phosphate. All of the urethral stones contained 30–60% struvite, which indicates an infection with urease-producing organisms. Calcium oxalate was detected in three of 20 stones.[22]

PATHOGENESIS

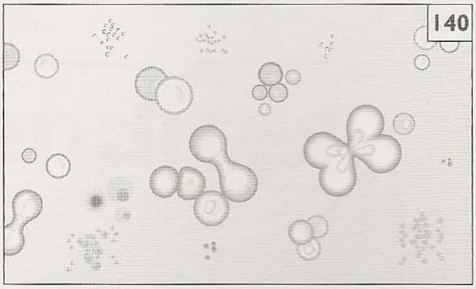
Lithogenesis in guinea pigs is comparable to that seen in rabbits, and reference is therefore made to pp. 134–7. Feeding trials have demonstrated a high level of intestinal absorption of calcium (80%) and phosphate (50%) in guinea pigs.[312] The anatomical conditions, especially in female animals, lead primarily to the deposit of crystals, which can then trigger an infection. Urethral stones therefore contain a relatively high proportion of struvite. However, the basic type of stone formation in guinea pigs is a sterile urolithiasis with calcium carbonate stones.

There are no specific measures for the diagnosis (**141, 142**), treatment and prevention of recurrence in guinea pigs; one may therefore proceed according to the remarks relating to rabbits (see pp. 134–7).

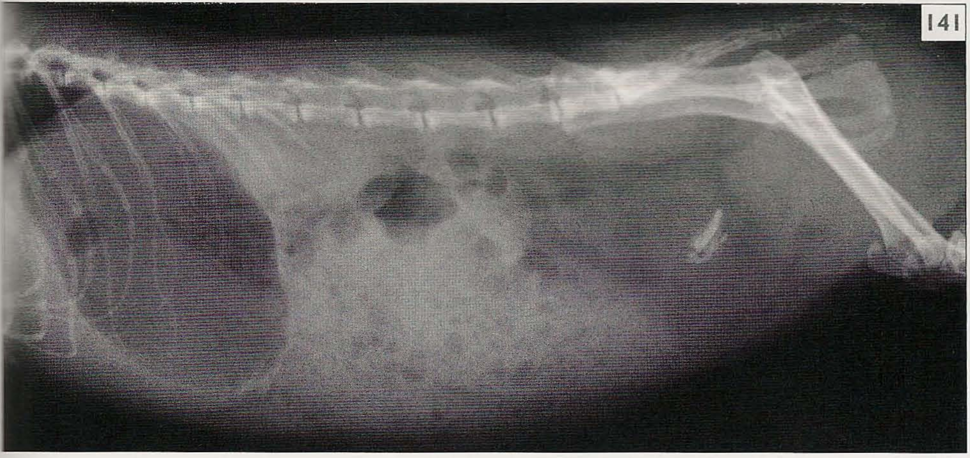
139



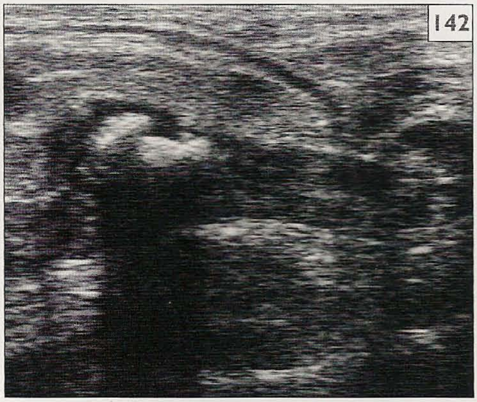
139 Fragments of uroliths of a guinea pig. Infrared spectrum analysis showed 60% calcite and 40% amorphous calcium phosphate.



140 Various forms of calcite crystals in urine sediment (drawing).



141 Abdominal radiograph of a guinea pig with several radiopaque bladder stones,



142 Ultrasound scan of the bladder of the guinea pig in **141**. The stone can be easily distinguished by its acoustic shadow.

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Appendices

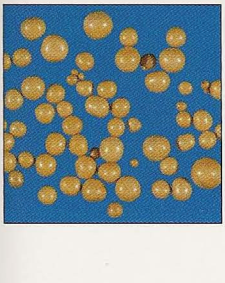
Urinary stones in other animals

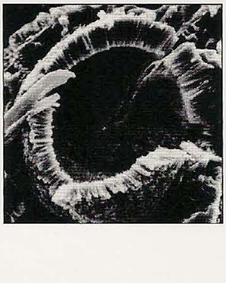
Calcium content of foodstuffs

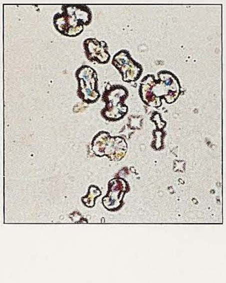
Oxalate content of foodstuffs

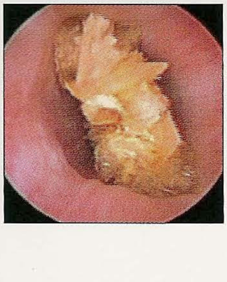
Purine content of foodstuffs

Methionine content of foodstuffs









Urinary stones in other animals

According to the literature, the pathological formation of concretions in the urinary organs is to be expected in all animal species (**143**). *Table 45* gives an overview of the types of stone found in different species.[8,40,313-317]

143 Multiple small stones from a goat (analysis: calcite – calcium carbonate).

Table 45 Types of urinary stones in various animal species.

Animal species	**Type of stone**
Horse, donkey	Calcium carbonate, calcium phosphate
Cattle	Calcium carbonate, struvite, silicate, calcium oxalate
Pig	Calcium phosphate, struvite, calcium oxalate
Sheep	Struvite, calcium phosphate, silicate
Goat	Calcium oxalate, struvite, calcium carbonate
Bird	Uric acid, urates
Mustelids	
- American mink	Struvite
- Ferret	Struvite
Otters	
- Oriental small-clawed otter	Calcium oxalate
- Eurasian river otter	Ammonium urate
Tortoise	Urates, phosphates
Crocodile, snake	Urates
Dromedary, camel	Silicate, calcium carbonate
Llama	Silicate, calcium carbonate
Deer	Matrix stones, calcium oxalate
Maned wolf	Cystine
Elephant seal/sea lion	Urates

Calcium content of foodstuffs[325]

LOW CALCIUM CONTENT (<150 mg/100 g)

Product	Calcium (mg/100 g)	Portion (g)	Calcium (mg/portion)
Butter	20	10	-
Cream	90	40	36
Coffee cream	100	10	10
Fromage frais, fruit fromage frais			
Low fat–20% fat	90	50	45
30–50% fat	80	50	40
60–70% fat	70	50	35
Full fat cream cheese (70% fat)	70	30	20
Sour cream, crème fraiche	100	15	15
Cottage cheese (20% fat)	100	50	50
Fresh milk, UHT milk, milk shakes, buttermilk, whey	120	200	240
Yoghurt, kefir	120	150	180
Blancmange, rice pudding	120	175	210
Sour milk cheese	120	40	50
Ice cream	150	30	45

MEDIUM CALCIUM CONTENT (151–400 mg/100 g)

Product	Calcium (mg/100g)	Portion (g)	Calcium (mg/portion)
Condensed milk	250	10	25
Wholegrain low fat yoghurt			
Three-grain fruit yoghurt			
Six-grain fruit yoghurt	250–280	150	380–420
Low-fat three-grain muesli yoghurt			
Low-fat three-grain fruit yoghurt			
Camembert, brie			
60–70% fat	300	40	120
45% fat	400	40	160

HIGH CALCIUM CONTENT (>400 mg/100 g)

Product	Calcium (mg/100 g)	Portion (g)	Calcium (mg/portion)
Blue cheese	500	40	200
Feta (sheep cheese)	600	40	240
Butter cheese, Cheshire, Edam, Gouda, Maasdam, Tilsit Processed cheese (30% fat)	800	50	400
Hard cheese			
Emmental	1,200	50	600
Parmesan	1,300	15	200
Parmesello	1,600	15	240
Full-fat milk powder	900	10	90
Milk protein powder			
60% protein	1,900	10	190
80% protein	1,400	10	140
Whey protein powder			
40% protein	700	10	70
80% protein	500	10	50

Oxalate content of foodstuffs[319,320,321]

LOW OXALATE CONTENT (<10 mg/100 g)

Product	Oxalic acid (mg/100 g)	Portion (g)	Oxalic acid (mg/portion)
Fruit			
Watermelon, apples, oranges, pears, cherries, peaches, pineapple	0.3–4.9	100	0.3–4.9
Bananas, apricots, plums, mandarins	6.8–8.5	100	6.8–8.5
Vegetables			
Peas, cooked	0.2	150	0.3
Lettuce	0.3	50	0.2
Cucumbers	0.4	150	0.6
Cauliflower	0.4	150	0.6
Brussel sprouts, cooked	1.2	150	1.8
Broccoli, cooked	1.4	150	2.1
Asparagus, cooked	2.6	250	6.5
Savoy cabbage, cooked	3.5	150	5.3
Fennel, cooked	5.3	150	8.0
Sauerkraut, raw	7.1	150	10.7
Tomatoes	8.5	150	12.8
Salsify, tinned	9.1	150	13.7
Milk	0.4	150	0.6
Drinks			
Coffee	0.6	150 ml	0.9
Fruit tea	0.6	150 ml	0.9
Beer, wheat beer	1.8	200 ml	3.6
Black tea	4.0	150 ml	6.0

MEDIUM OXALATE CONTENT (10–50 mg/100 g)

Product	Oxalic acid (mg/100 g)	Portion (g)	Oxalic acid (mg/portion)
Fruit			
Raspberry	18.9	100	18.9
Redcurrant	19.8	100	19.8
Fig	20.5	100	20.5
Red gooseberry	21.6	100	21.6
Kiwi	23.0	100	23.0
Blackberry	29.2	100	29.2
Vegetables			
Lentils, dried	13.3	100	13.3
Aubergine	16.2	150	24.3
Leeks	17.0	150	24.3
Carrots	17.8	150	26.7
Potatoes, cooked	24.3	150	36.5
Olives, green	45.7	20	9.1
Beans, white, tinned	54.2	150	81.3
Bread			
Toast	11.8	50	5.9
Rolls	20.3	50	10.2
Mixed wheat bread	24.8	50	12.4
Wholemeal rye bread	32.2	50	16.1
Wholemeal rye crisp bread	49.5	50	24.8

HIGH OXALATE CONTENT (>50 mg/100 g)

Product	Oxalic acid (mg/100 g)	Portion (g)	Oxalic acid (mg/portion)
Beetroot	160	150	240
Almonds	383	100	383
Wheat bran	457	30	137
Cocoa powder	567	50	284
Swiss chard	874	150	1,311
Rhubarb	1,235	150	1,853
Sorrel	1,391	100	1,391
Spinach	1,959	150	2,939

Purine content of foodstuffs[322,324]

Calculated as generated uric acid

- Up to 50 mg uric acid: low purine content
- 51–150 mg: medium purine content
- >150 mg: high purine content

Foodstuff	Uric acid (mg/100 g)	Portion (g)	Uric acid (mg/portion)
Eggs, milk and dairy products			
Whole egg (chicken)	5	60	3
Butter	0	10	0
Full-fat milk	0	200	0
Yoghurt, 3.5% fat	0	150	0
Fromage frais, 20% fat	0	150	0
Emmental, 45 % fat	10	50	5
Camembert, 45% fat	30	50	15
Fruit			
Pineapple	20	150	30
Apple	15	150	23
Orange	20	150	30
Banana	25	150	38
Pear	15	150	23
Strawberries	25	150	38
Grapefruit	15	150	23
Raspberries	18	150	27
Kiwi	19	150	29
Peach	18	150	27
Cherries	15	150	23
Water melon	20	150	30
Grapes	20	150	30
Damsons	20	150	30
Vegetables			
Cauliflower	45	200	90
Broccoli	50	200	100
Fennel	16	200	32
Gherkins	15	50	8
Potatoes	15	200	30
Kohlrabi	30	200	60
Lettuce	10	50	5

Foodstuff	Uric acid (mg/100 g)	Portion (g)	Uric acid (mg/portion)
Vegetables (continued)			
Leeks	40	200	80
Carrots	15	200	30
Red pepper	15	200	30
Brussel sprouts	60	200	120
Red cabbage	40	200	80
Cucumber	6	200	12
Sauerkraut	20	200	40
Salsify	70	200	140
Celeriac	30	200	60
Asparagus	25	200	50
Spinach	50	200	100
Tomatoes	10	200	20
Savoy cabbage	40	200	80
Courgettes	20	200	40
Onions	15	50	8
Pulses			
Beans, green, fresh	42	200	84
Peas, green, fresh	150	200	300
Lentils, dried	200	50	100
Soy beans, dried	370	50	185
Tofu	70	150	105
Seeds and nuts			
Peanuts	70	50	35
Hazelnuts	40	50	20
Almonds	40	50	20
Sunflower seeds	160	50	80
Cereals and cereal produce			
Bread rolls	40	50	20
Egg pasta, cooked	22	200	44
Spelt	125	50	63
Millet	117	50	59
Mixed grain bread	45	50	23
Rye wholemeal bread	50	50	25
Brown rice, cooked	35	50	18

Foodstuff	**Uric acid (mg/100 g)**	**Portion (g)**	**Uric acid (mg/portion)**
Cereals and cereal produce (*continued*)			
Wheat crisp bread	100	20	20
Wheat wholemeal bread	60	50	30
Mushrooms			
Oyster mushrooms, fresh	90	200	180
Field mushrooms, fresh	60	200	120
Meat			
Chicken drumstick, uncooked	160	150	240
Veal, uncooked	150	150	225
Turkey escalope, uncooked	120	150	180
Beef, uncooked	140	150	210
Pork escalope, uncooked	170	150	255
Offal			
Sweetbread, veal, uncooked	900	100	900
Pork liver, uncooked	300	150	450
Pork kidney, uncooked	255	150	383
Meat products			
Hot dog sausage	110	100	110
Smoked ham	180	100	180
Boiled ham	130	100	130
Liver sausage	140	50	70
Fish			
Anchovies, sardines	260	50	130
Halibut, skinned	170	150	255
Herring, with skin	320	250	480
Herring, skinned	290	150	285
Sardines in oil	350	100	350
Haddock, skinned	130	150	195
Plaice, skinned	130	150	195
Sprats	500	100	500
Drinks			
Apple juice	8	150	12
Beer, alcohol-free	10	500	50
Beer, with alcohol	15	500	75
Coffee (drink)	0	150	0

Foodstuff	Uric acid (mg/100 g)	Portion (g)	Uric acid (mg/portion)
Drinks (*continued*)			
Grapefruit juice	10	150	15
Orange juice	12	150	18
Red wine	0	150	0
Sparkling wine	0	150	0
White wine	0	150	0
Tea (drink)	0	150	0

Methionine content of foodstuffs[323]

LOW METHIONINE CONTENT (<0.06 g/100 g)

Foodstuff	Methionine (g/100 g)	Portion (g)	Methionine (g/portion)
Fruit			
Generally very low in methionine			
Vegetables			
Tomatoes	0.007	150	0.011
Aubergines	0.007	150	0.011
Carrots	0.009	150	0.014
Onions	0.012	20	0.0024
Lettuce	0.012	50	0.006
White cabbage	0.013	150	0.02
Red cabbage	0.014	150	0.021
Kohlrabi	0.016	150	0.024
Red peppers	0.016	100	0.016
Asparagus	0.027	150	0.041
French beans	0.030	150	0.045
Potatoes	0.031	150	0.047
Spinach	0.043	150	0.072
Brussel sprouts	0.047	150	0.071
Kale	0.048	150	0.072
Peas	0.052	150	0.078
Corn	0.055	50	0.028
Mushrooms			
Chanterelles	0.008	50	0.004
Field mushrooms	0.023	50	0.012
Fats			
Margarine	0.006	20	0.001
Butter	0.019	20	0.004

MEDIUM METHIONINE CONTENT (0.06–0.3 g/100 g)

Foodstuff	Methionine (g/100 g)	Portion (g)	Methionine (g/portion)
Milk			
Milk	0.084	200	0.17
Buttermilk	0.082	200	0.164
Bread and bakery produce			
General	0.11–0.15	50	0.055–0.075
Cereal-based foodstuffs			
Cornflakes	0.13	50	0.065
Rice	0.13	50	0.065
Oat porridge (uncooked)	0.20	50	0.10
Egg pasta	0.20	100	0.20
Nuts			
Coconut	0.07	50	0.035
Hazelnuts	0.16	50	0.08
Walnuts	0.22	50	0.11
Almonds	0.26	50	0.13
Peanuts	0.28	50	0.24
Yeast	0.29		

HIGH METHIONINE CONTENT (>0.3 g/100 g)

Foodstuff	Methionine (g/100 g)	Portion (g)	Methionine (g/portion)
Veal			
Cutlet, fillet	0.47	150	0.71
Beef			
Roast beef	0.4	150	0.60
Rib roast	0.42	150	0.63
Pork			
Chop	0.40	150	0.60
Fillet	0.48	150	0.72
Kidneys	0.35	150	0.53
Liver	0.46	150	0.69

Foodstuff	Methionine (g/100 g)	Portion (g)	Methionine (g/portion)
Offal			
Processed meat			
Salami	0.38	30	0.12
Ham	0.44	30	0.13
Salami-type sausages	0.48	50	0.24
Corned beef	0.56	50	0.28
Poultry			
Roast chicken	0.54	150	0.81
Turkey	0.56	150	0.84
Fish			
Eel	0.43	50	0.22
Trout	0.49	150	0.74
Cod, plaice, haddock	0.50	150	0.75
Herring, mackerel, sardine	0.54	150	0.81
Salmon	0.59	50	0.30
Tuna	0.60	150	0.60
Halibut	0.68	150	1.02
Dairy			
Full-fat cream cheese	0.37	30	0.11
Camembert	0.47	30	0.14
Fromage frais	0.48	50	0.24
Emmental cheese	0.71	50	0.36
Eggs	0.68	60	0.41
Soy beans	0.64	100	0.64

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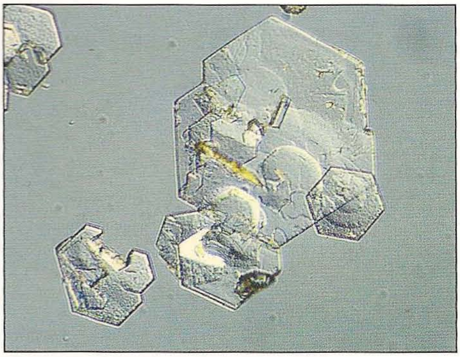

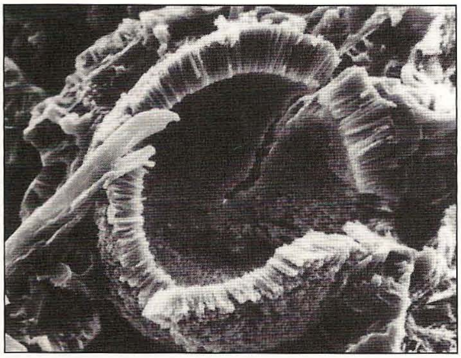

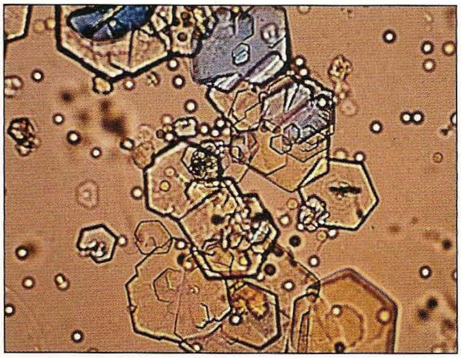

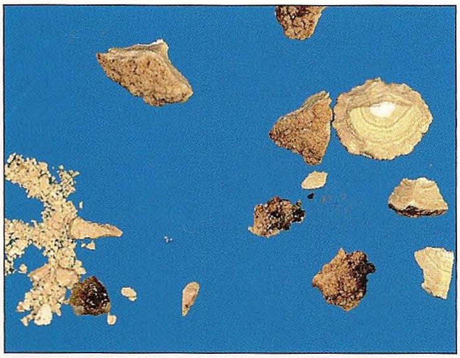

The Colour Handbook deals with all aspects of urolithiasis in dogs, cats, rabbits and guinea pigs – from aetiology and pathogenesis to diagnosis, treatment and the prevention of disease recurrence.

The authors introduce the reader to treatment protocols developed from their own research and experience, and incorporate international state-of-the-art knowledge of the disease. Topics covered in the Colour Handbook include:

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